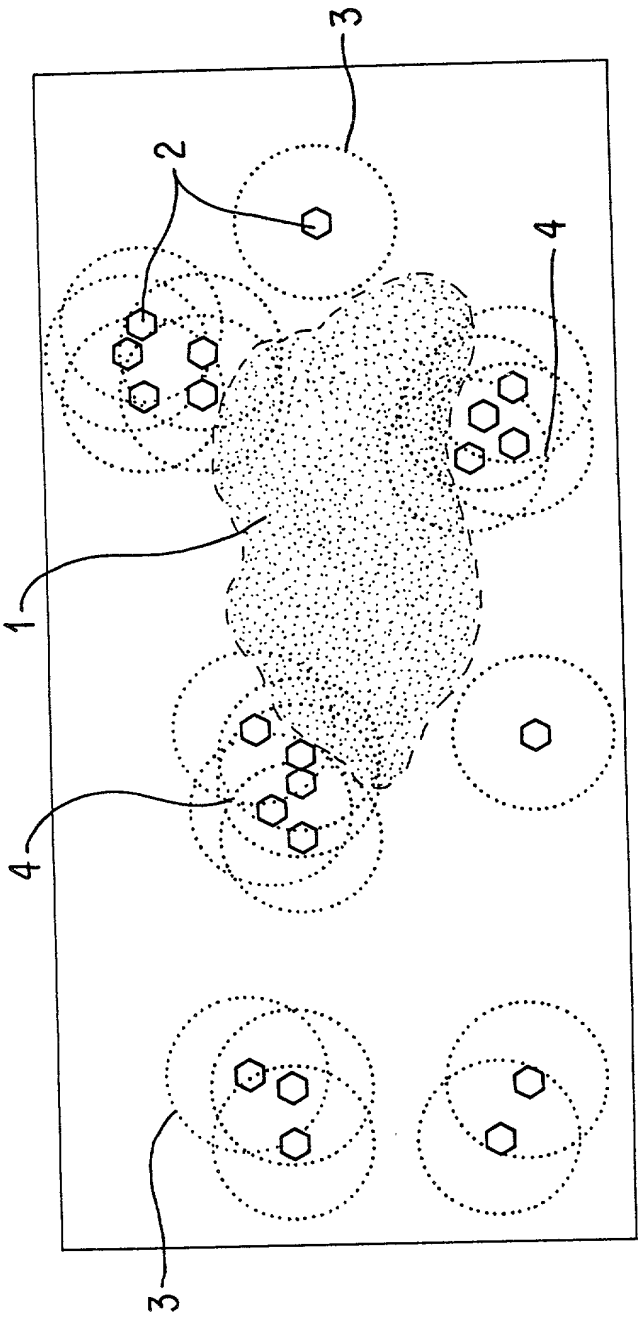


FIG. 1(a)

0 0 6 6 5 4 3 - 0 5 2 5 0 4

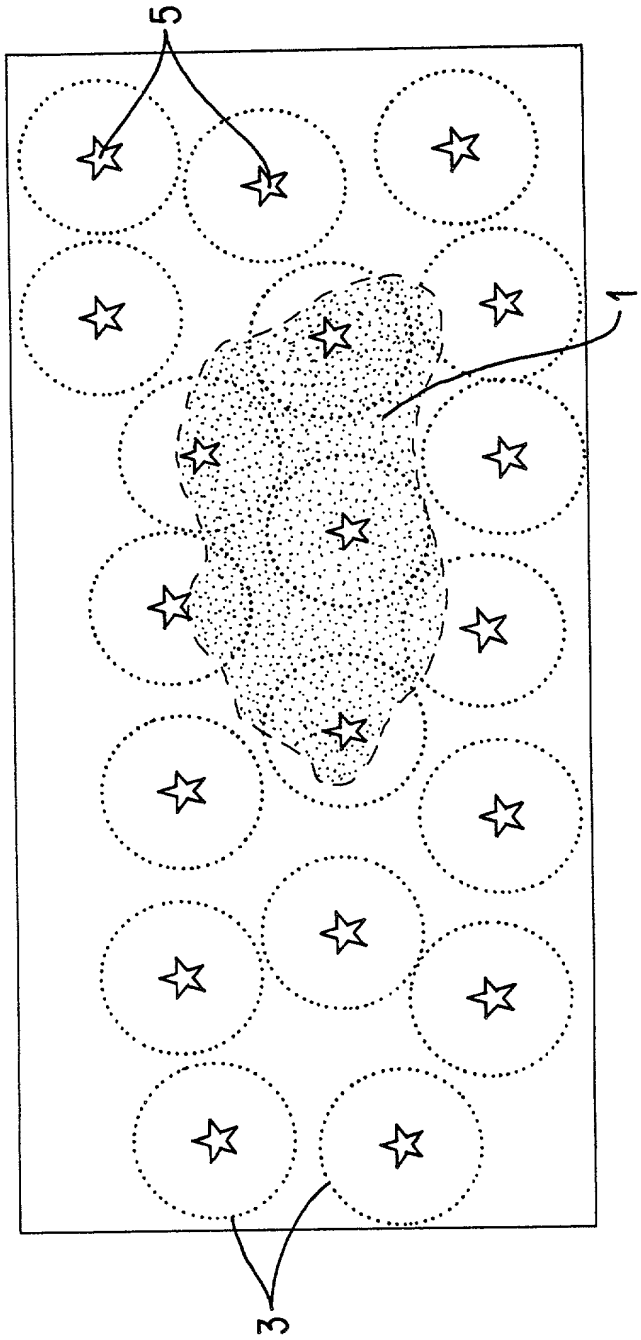


FIG.1(b)

0986528 - 050504

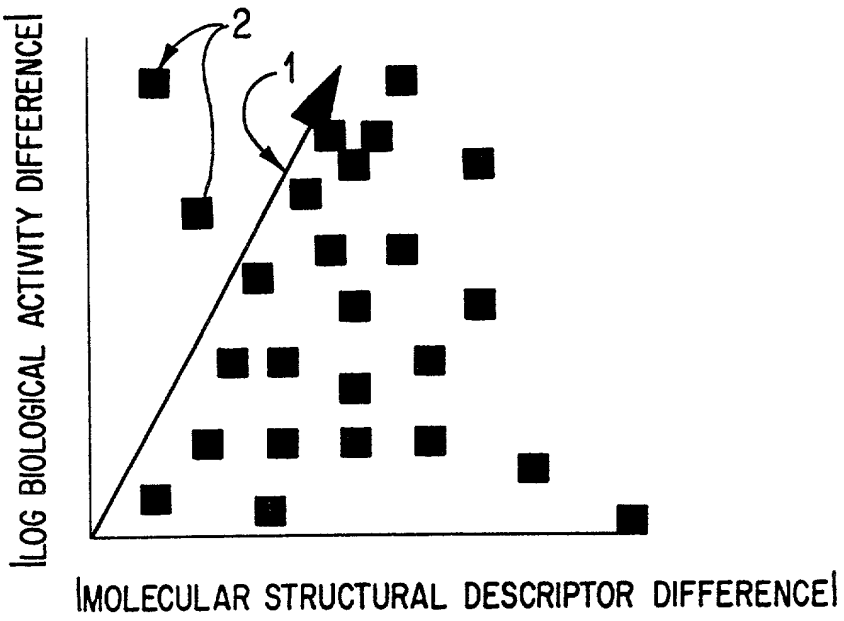
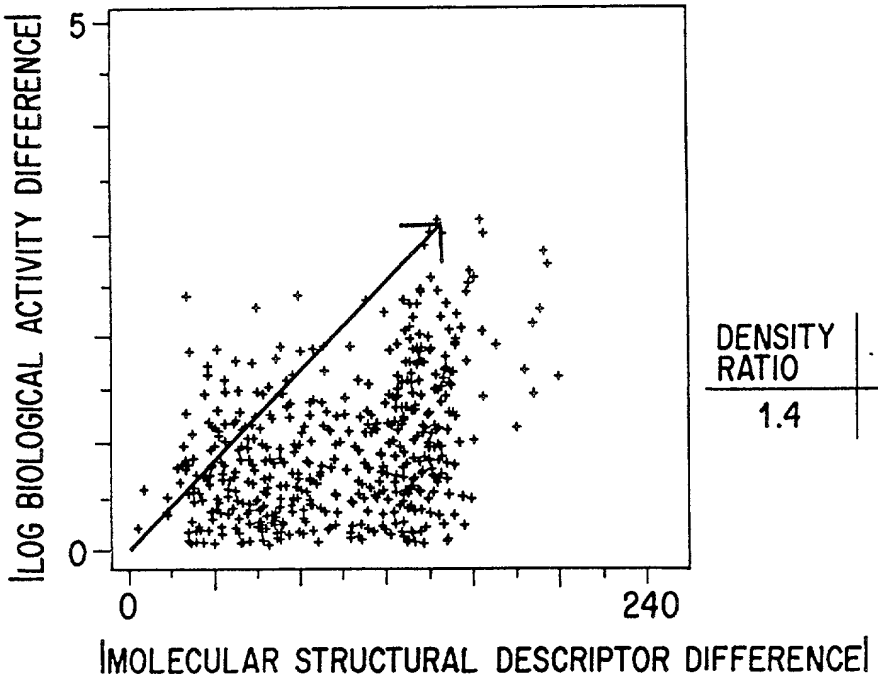


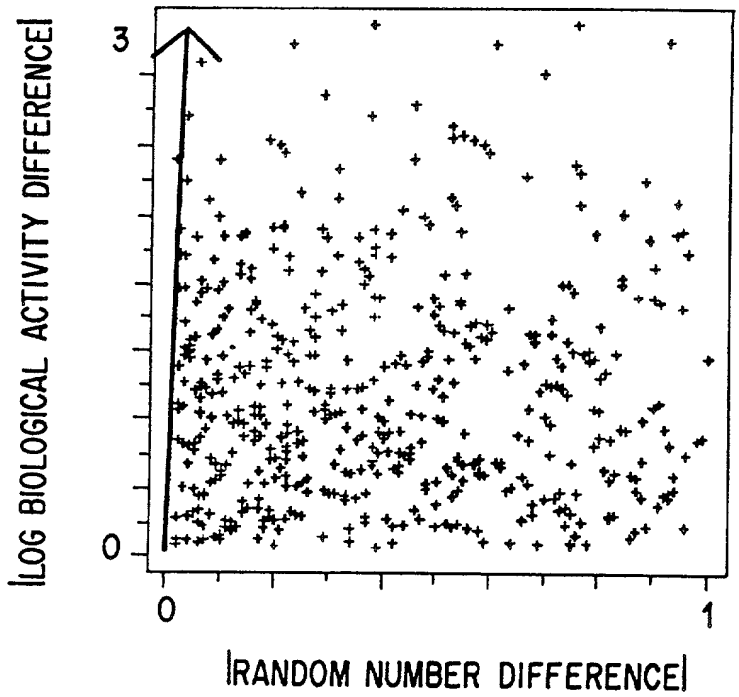
FIG. 2



DENSITY RATIO	χ^2
1.4	51.21

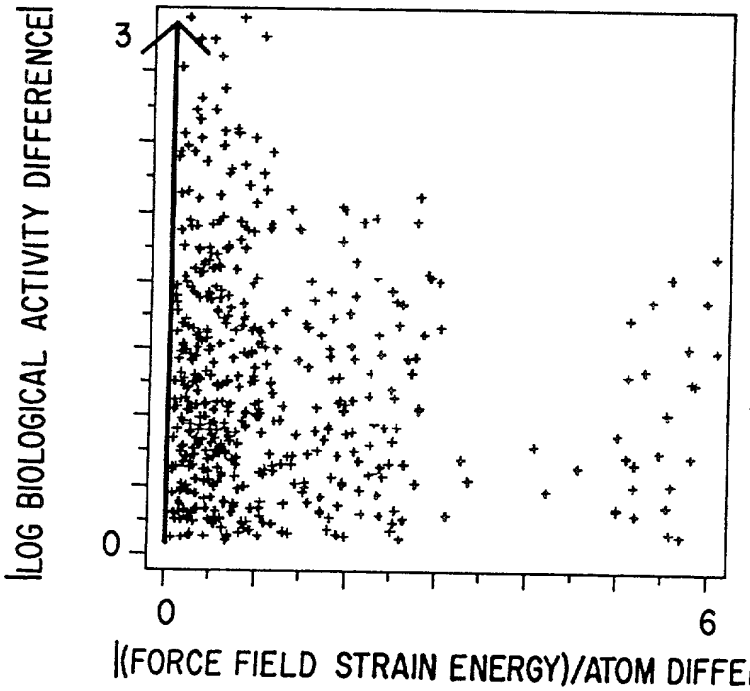
FIG. 3

EP 0 596 409 B1



DENSITY RATIO	χ^2
1.00	0.00

FIG. 4



DENSITY RATIO	χ^2
0.96	0.46

FIG. 5

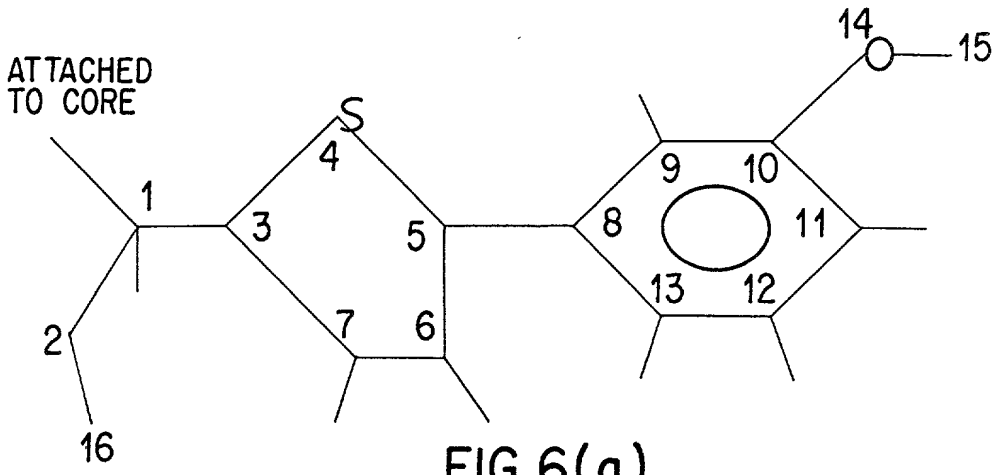


FIG. 6(a)

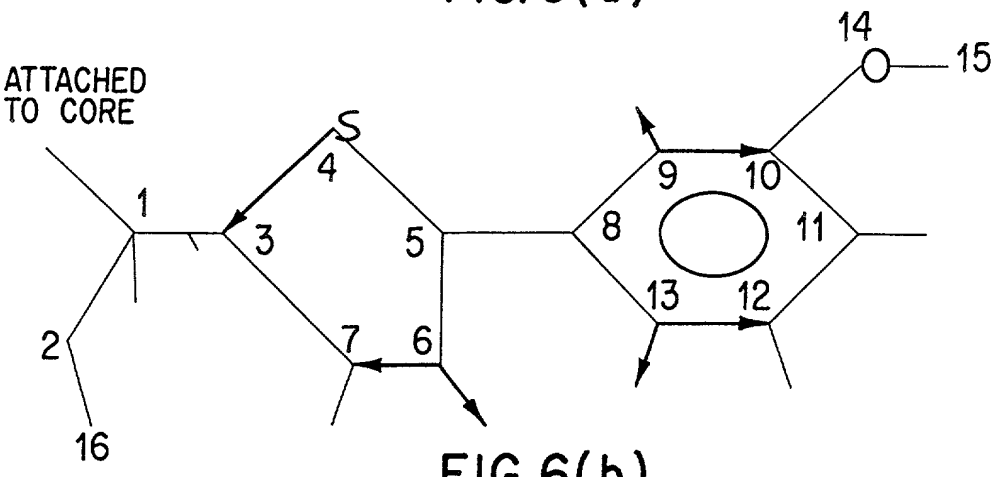


FIG. 6(b)

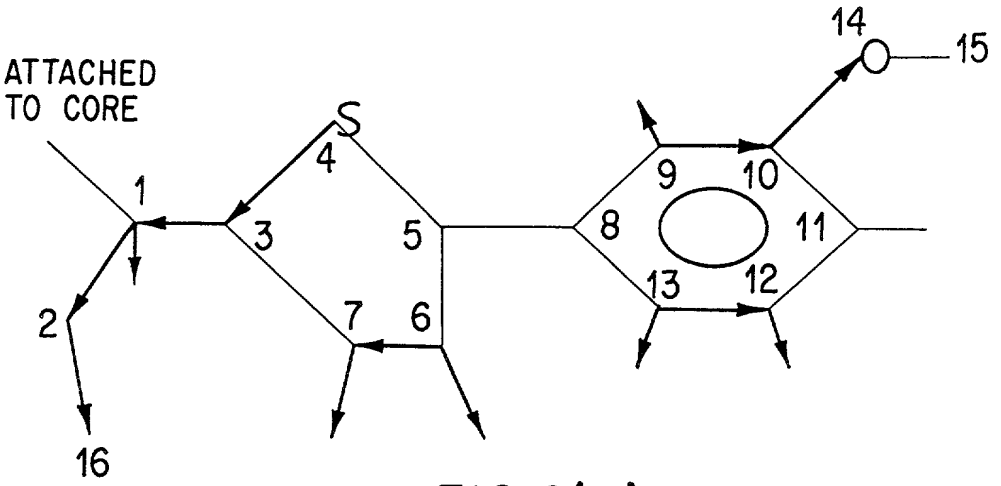


FIG. 6(c)

WO 95/25450 PCT/US95/03450

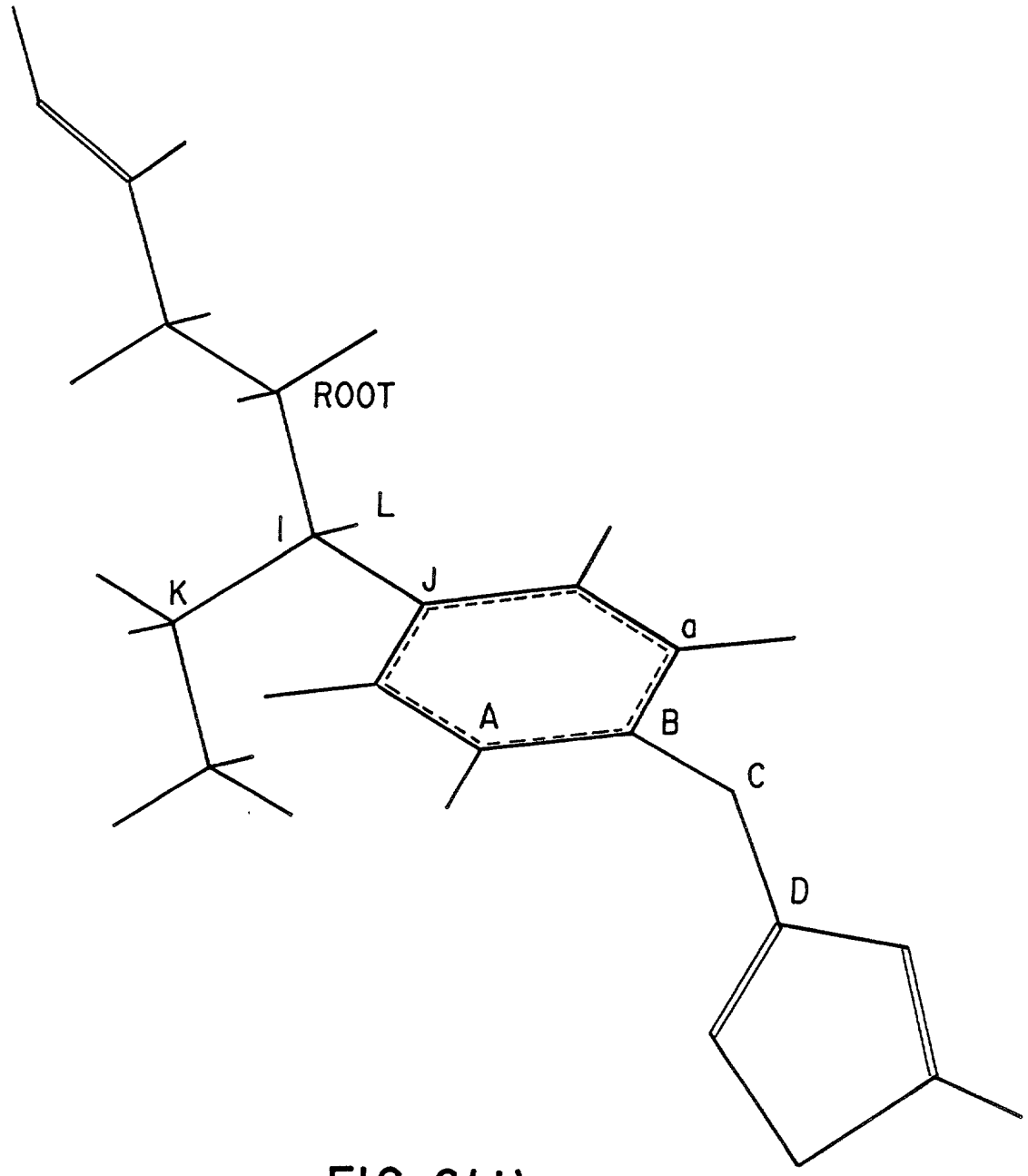


FIG. 6(d)

EP 0 595 548 A1

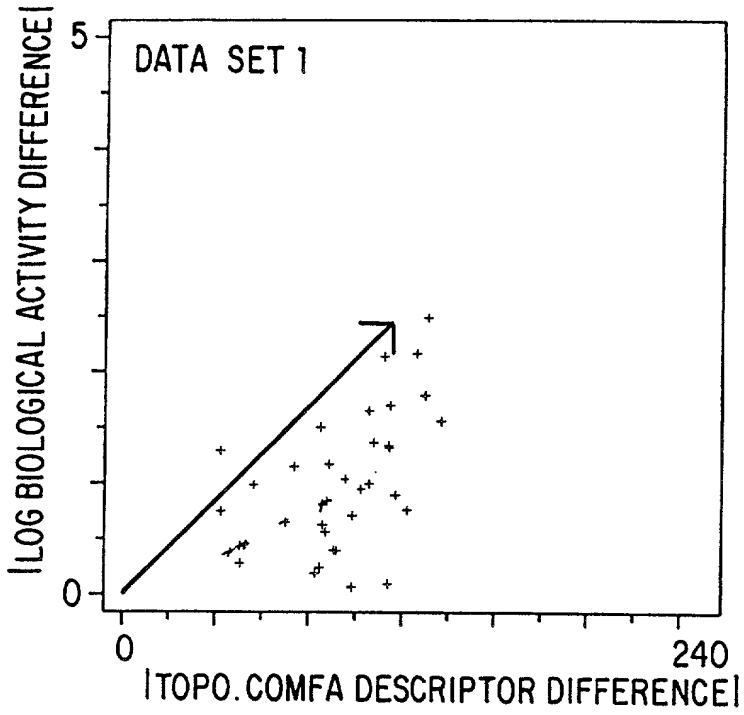


FIG.7(a)

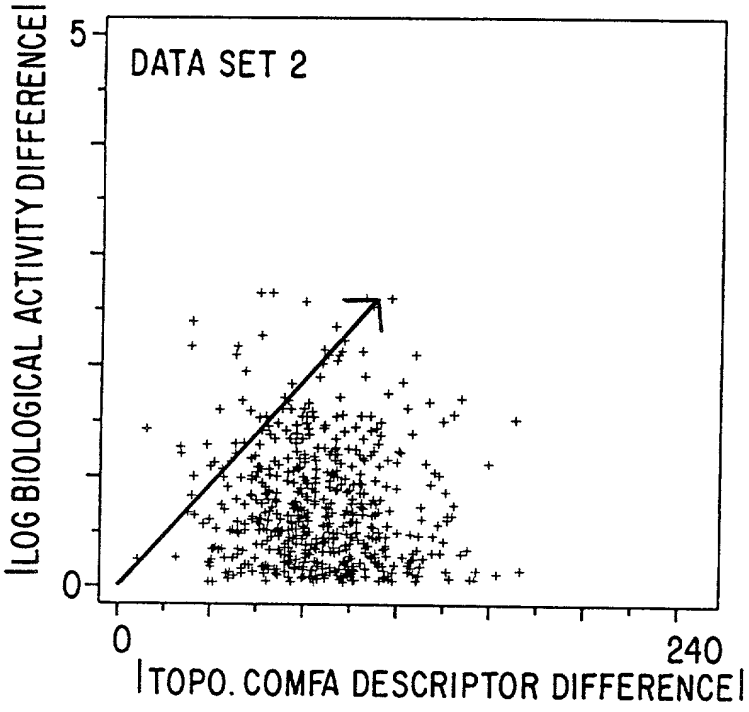


FIG.7(b)

WO 98/55548 PCT/US98/11501

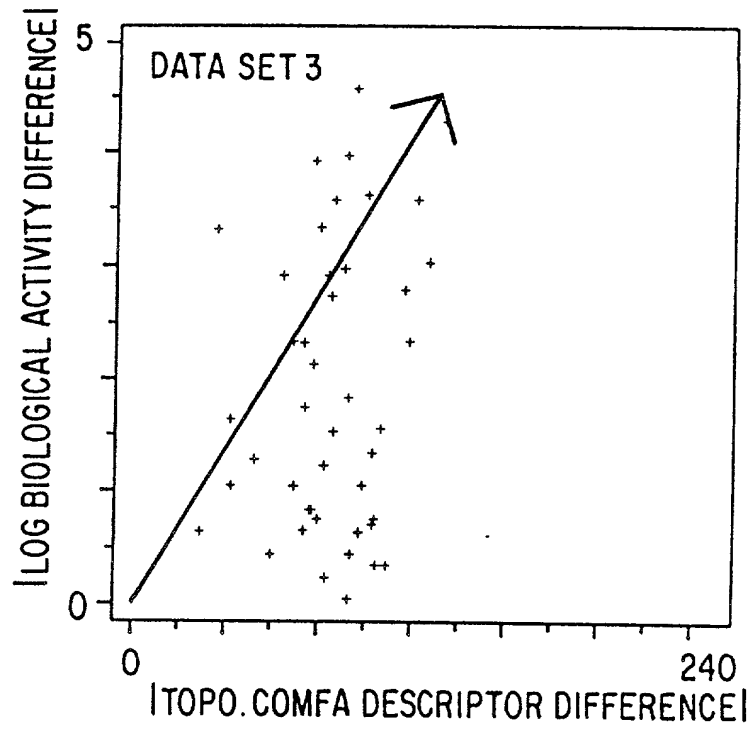


FIG. 7(c)

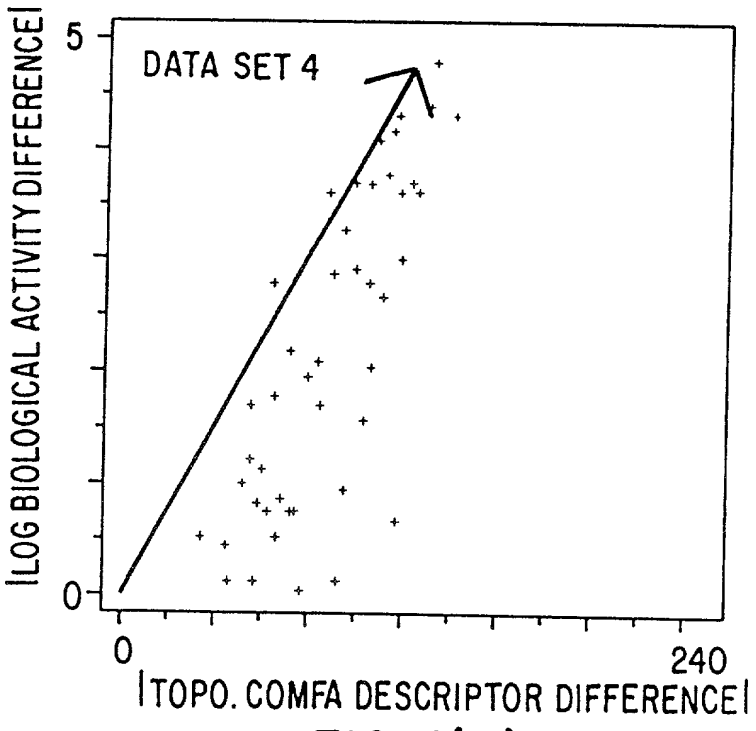


FIG. 7(d)

09655543 - 052504

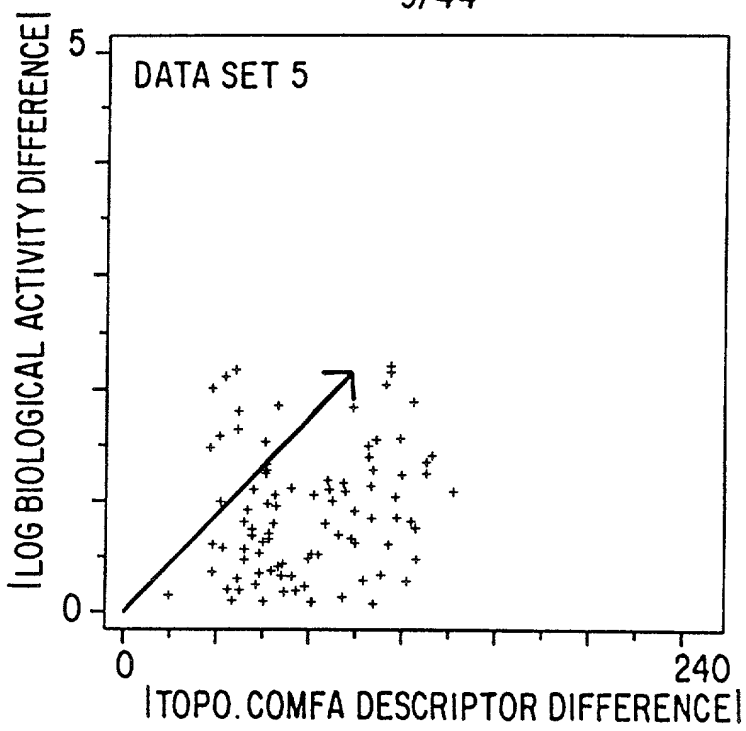

DATA SET 5
|LOG BIOLOGICAL ACTIVITY DIFFERENCE|
5
0
0
240
|TOPO. COMFA DESCRIPTOR DIFFERENCE|

FIG.7(e)

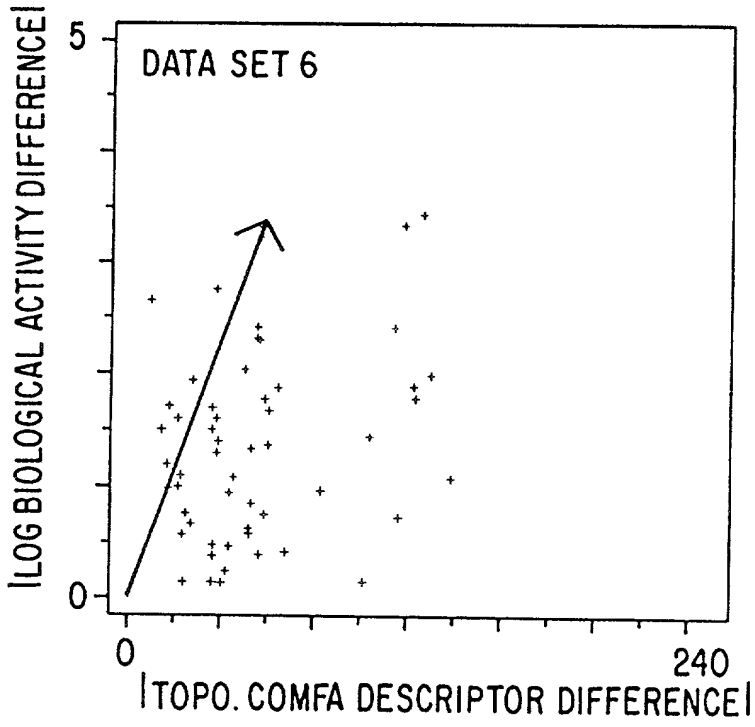

DATA SET 6
|LOG BIOLOGICAL ACTIVITY DIFFERENCE|
5
0
0
240
|TOPO. COMFA DESCRIPTOR DIFFERENCE|

FIG.7(f)

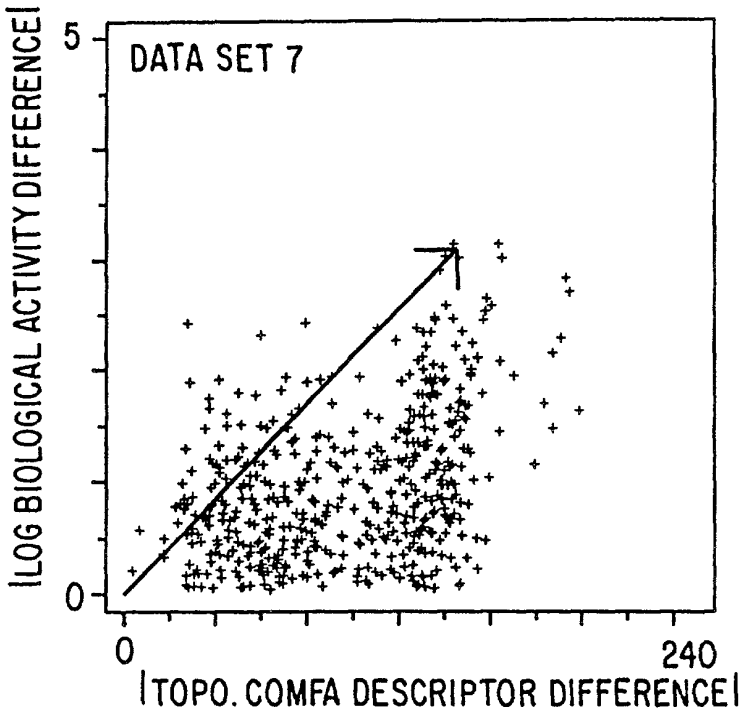


FIG.7(g)

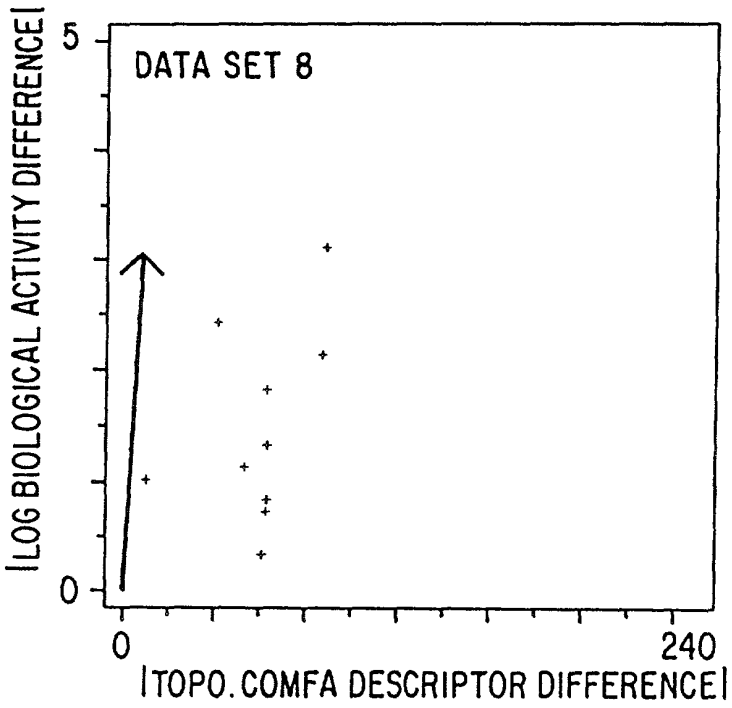


FIG.7(h)

0966548 .05550

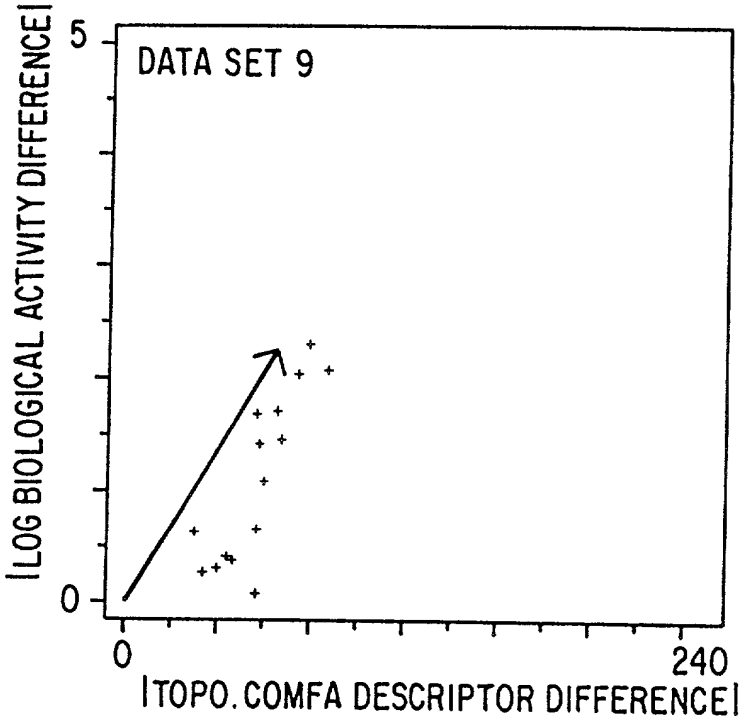


FIG. 7(i)

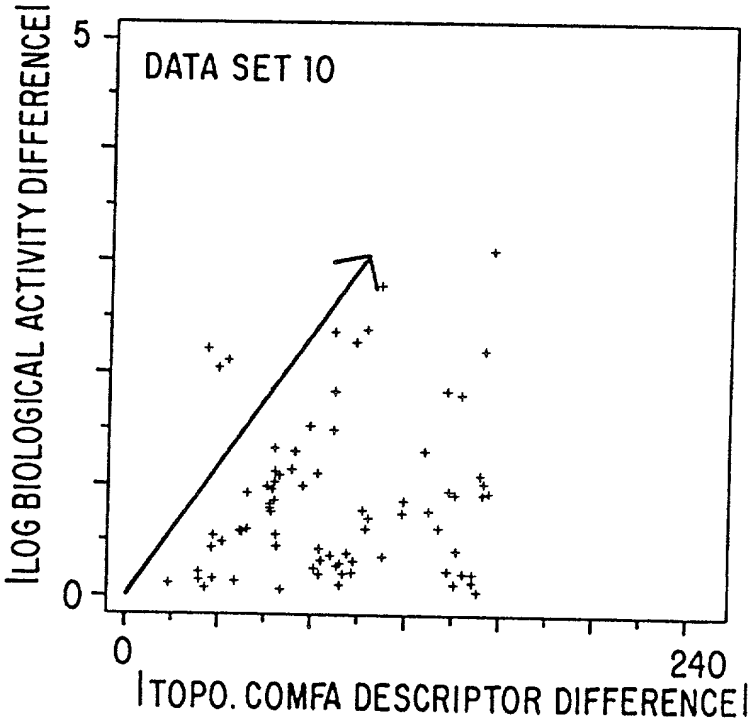


FIG. 7(j)

WO 96/36934 PCT/US96/06950

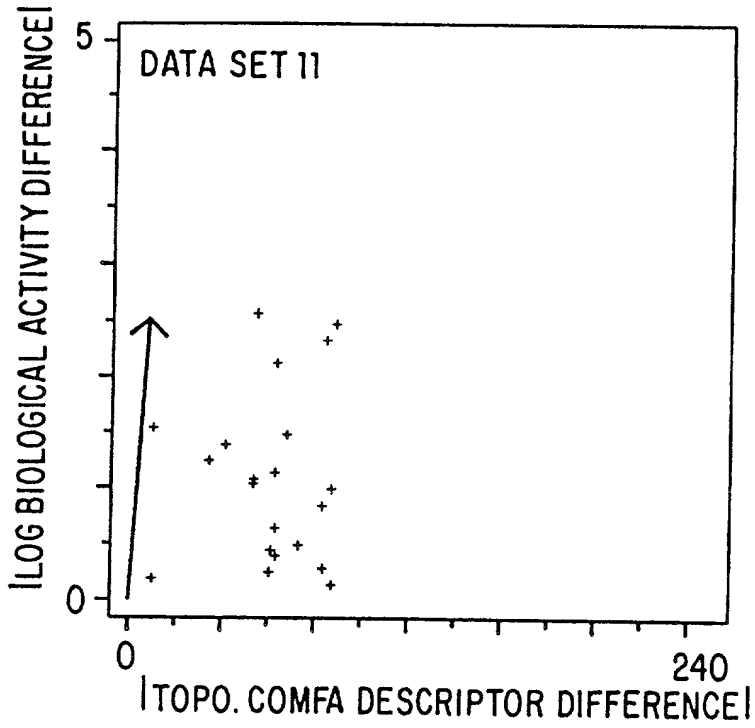


FIG.7(k)

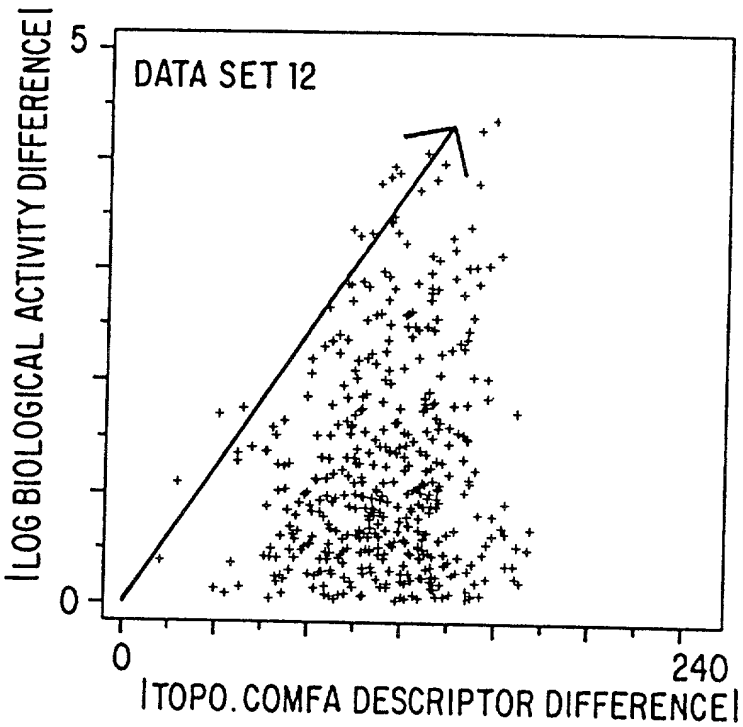


FIG.7(l)

0960543 - 050504

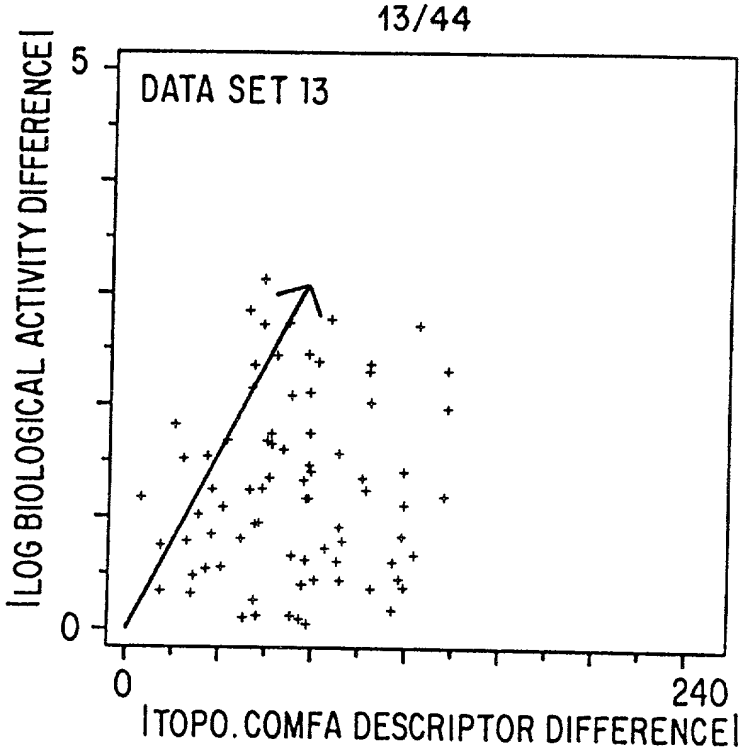


FIG. 7(m)

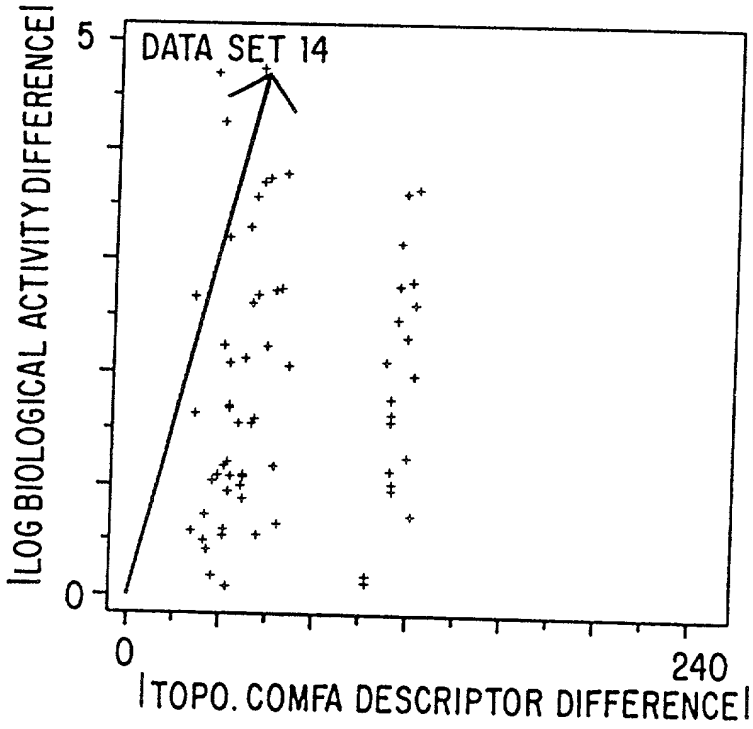


FIG. 7(n)

WO 95/06240 PCT/US94/09569

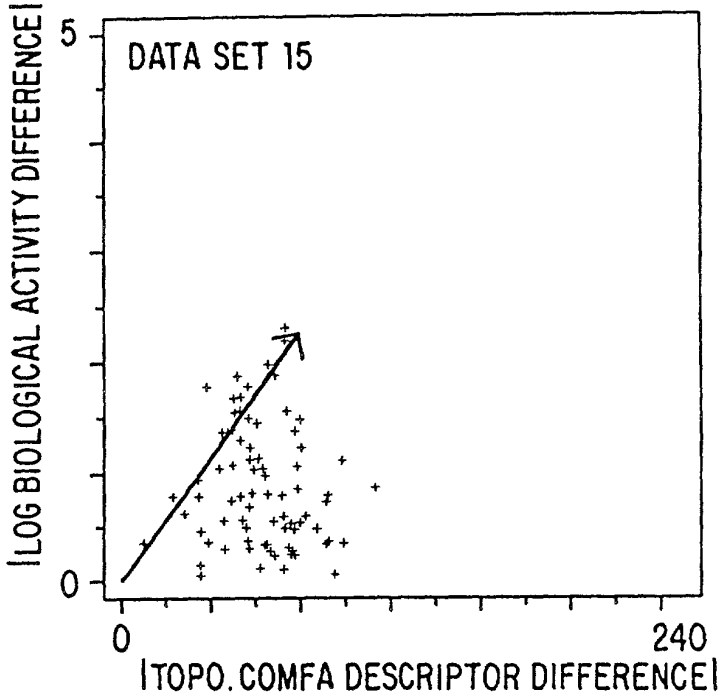


FIG.7(o)

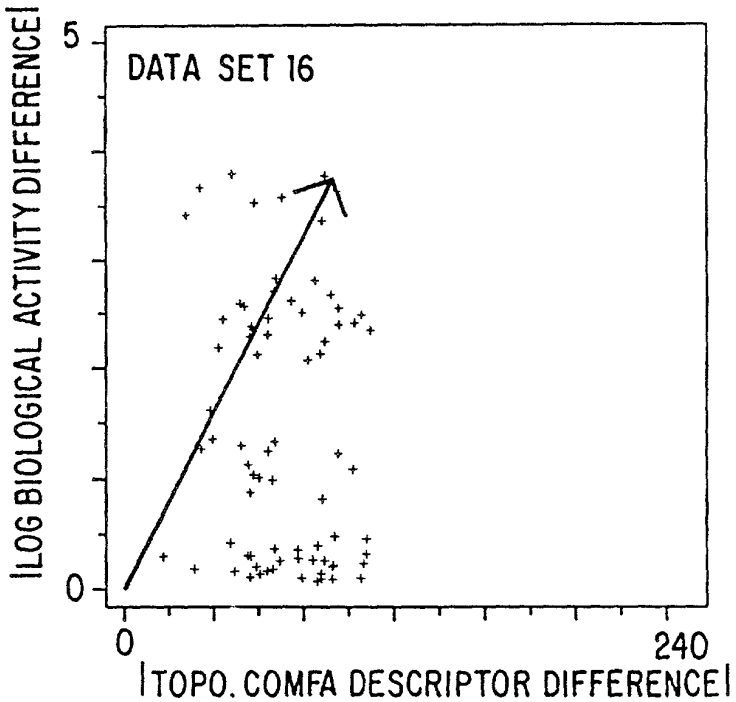


FIG.7(p)

0960548 - 050502

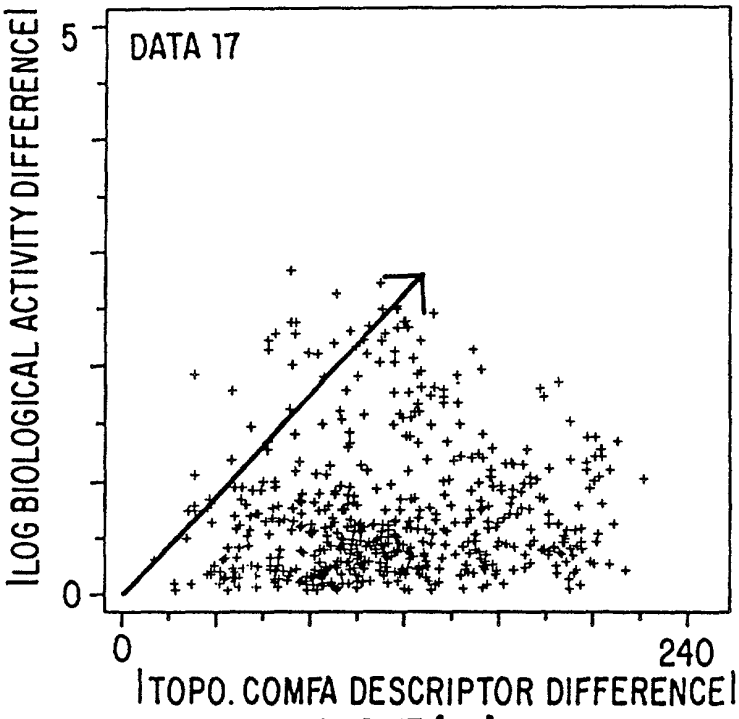


FIG.7(q)

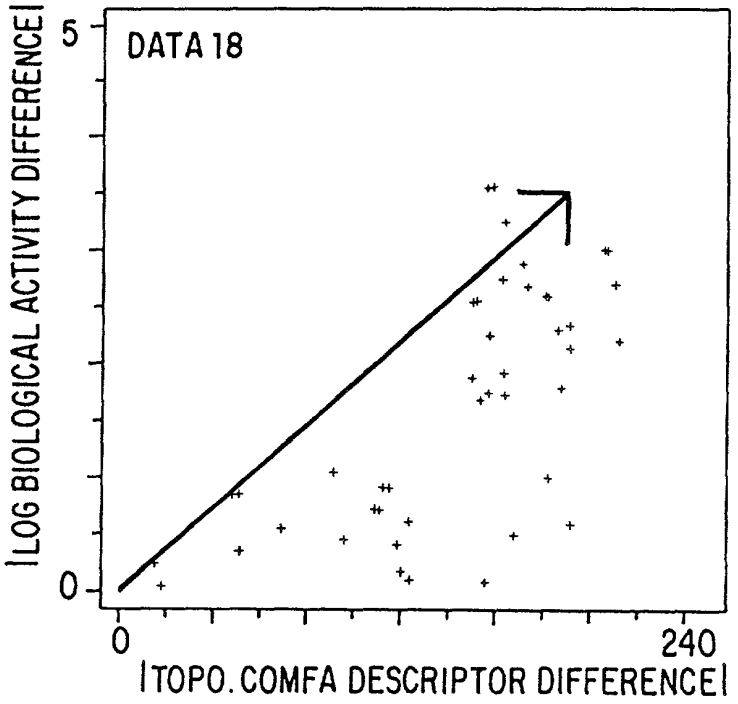


FIG.7(r)

0866543 - 052504

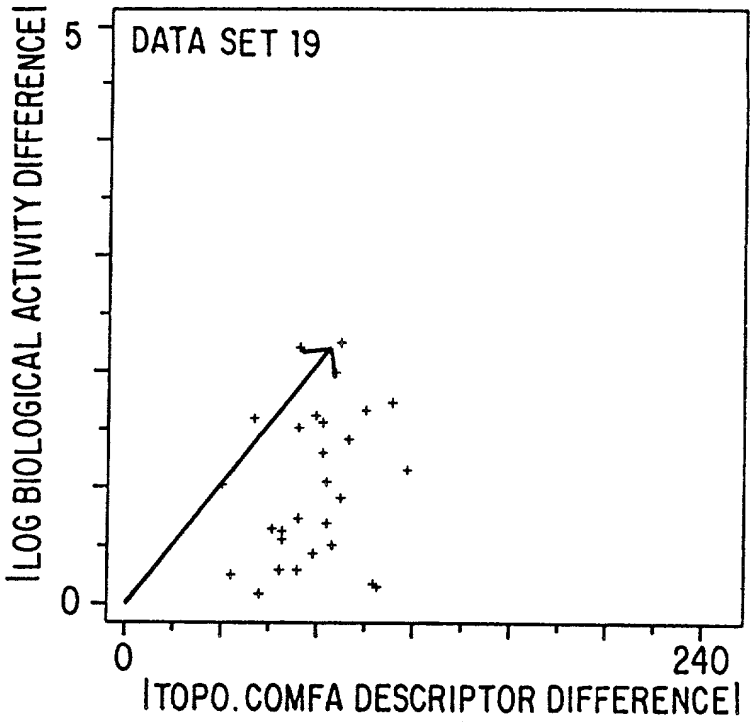

DATA SET 19
|LOG BIOLOGICAL ACTIVITY DIFFERENCE|
5
0
0
240
|TOPO. COMFA DESCRIPTOR DIFFERENCE|

FIG. 7(s)

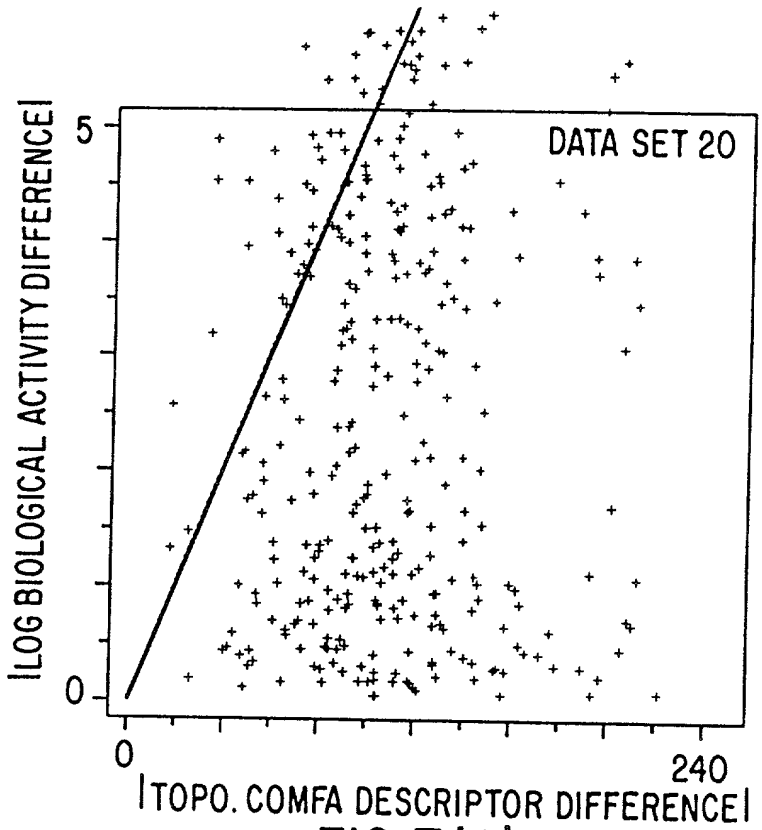

DATA SET 20
|LOG BIOLOGICAL ACTIVITY DIFFERENCE|
5
0
0
240
|TOPO. COMFA DESCRIPTOR DIFFERENCE|

FIG. 7(t)

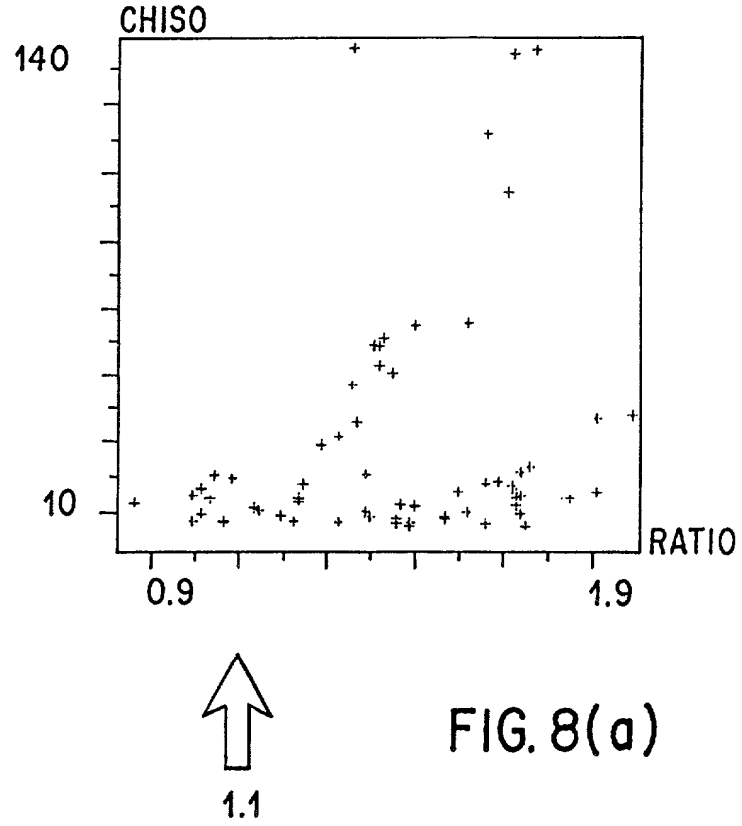


FIG. 8(a)

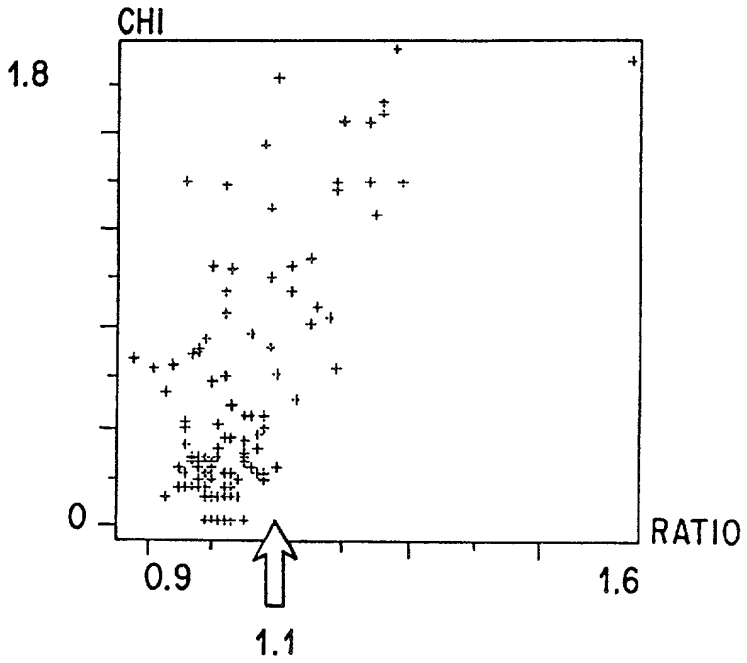


FIG. 8(b)

EP 0 595 545 B1

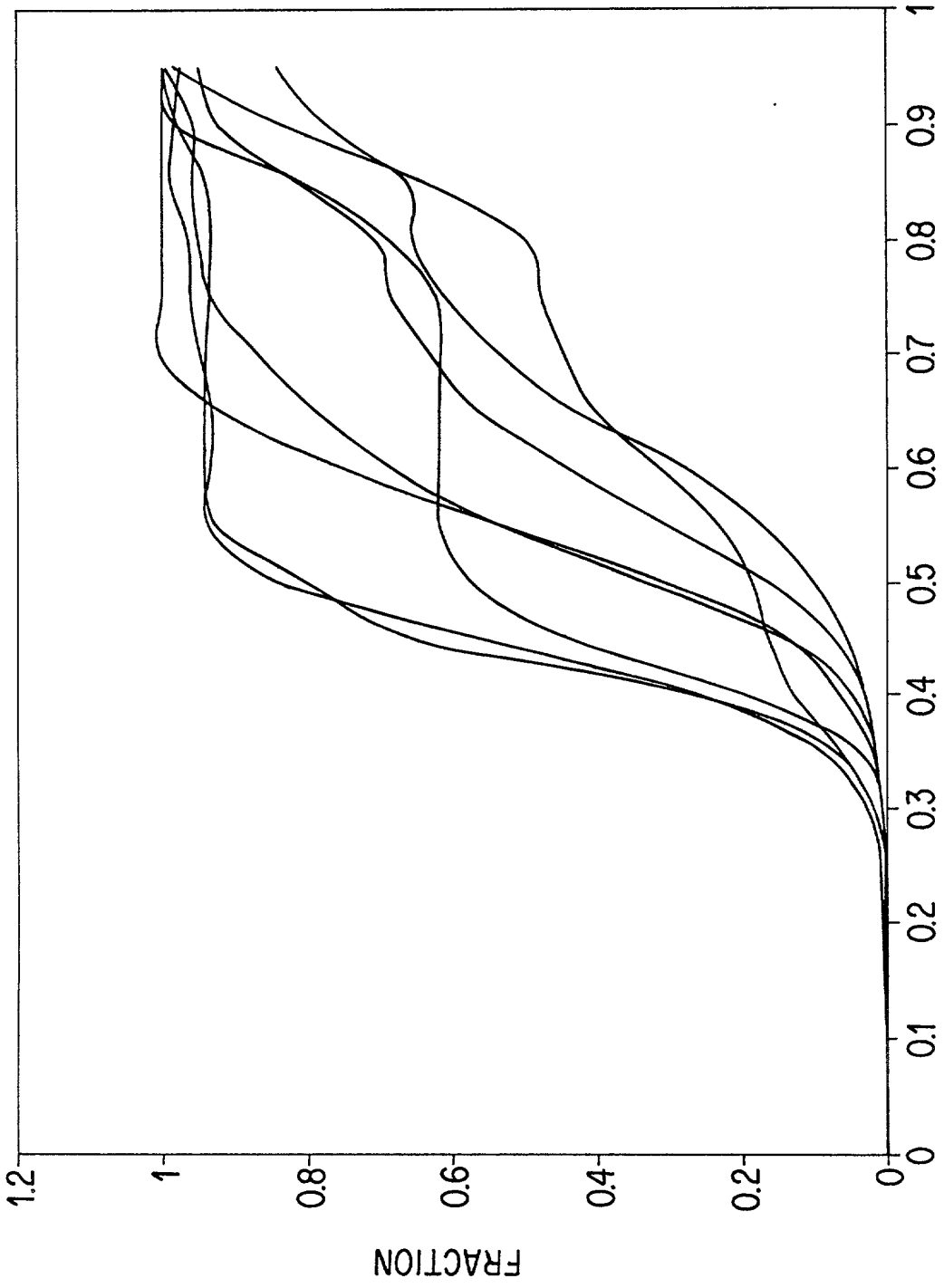


FIG. 9(a)

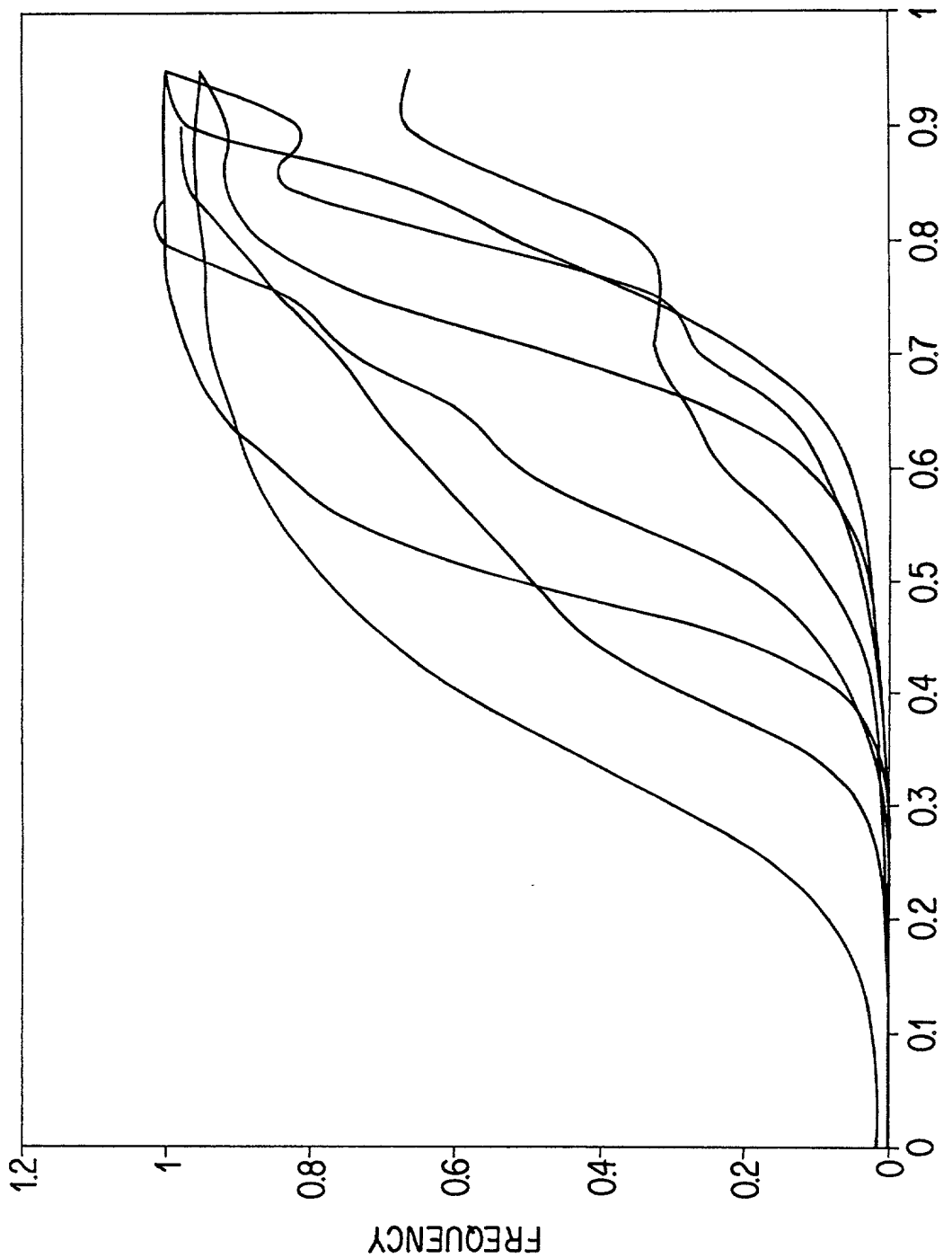


FIG. 9(b)

09865450 - 052504

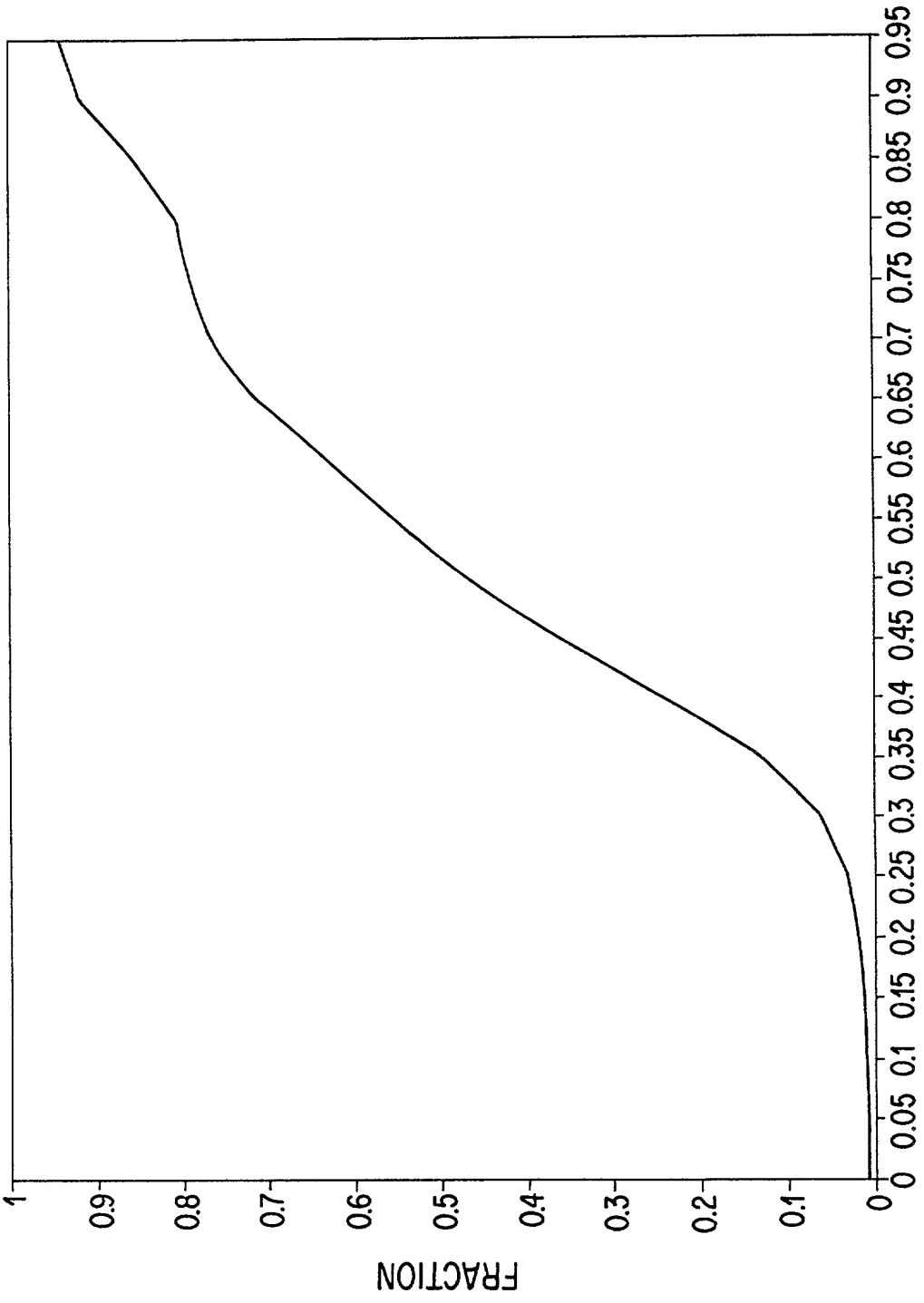


FIG.9(c)

Patent "0954880

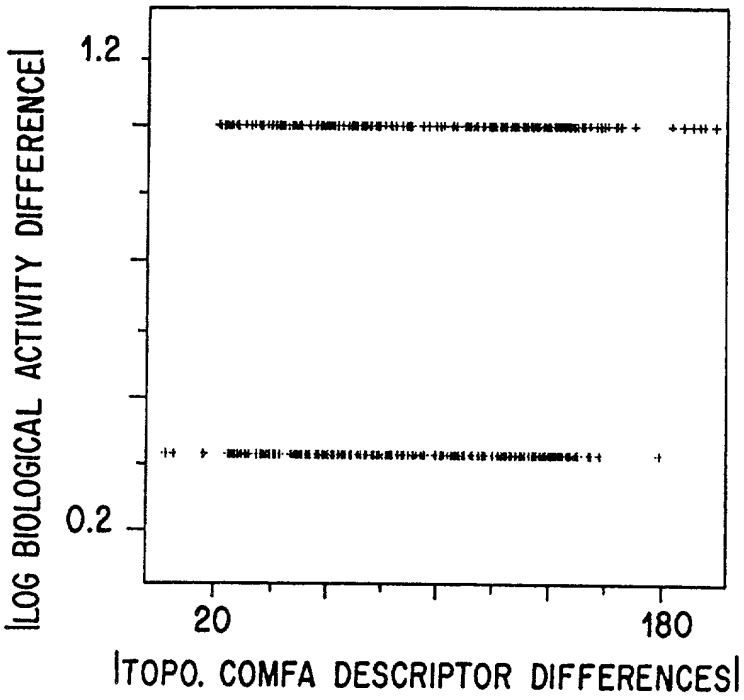


FIG. 10(a)

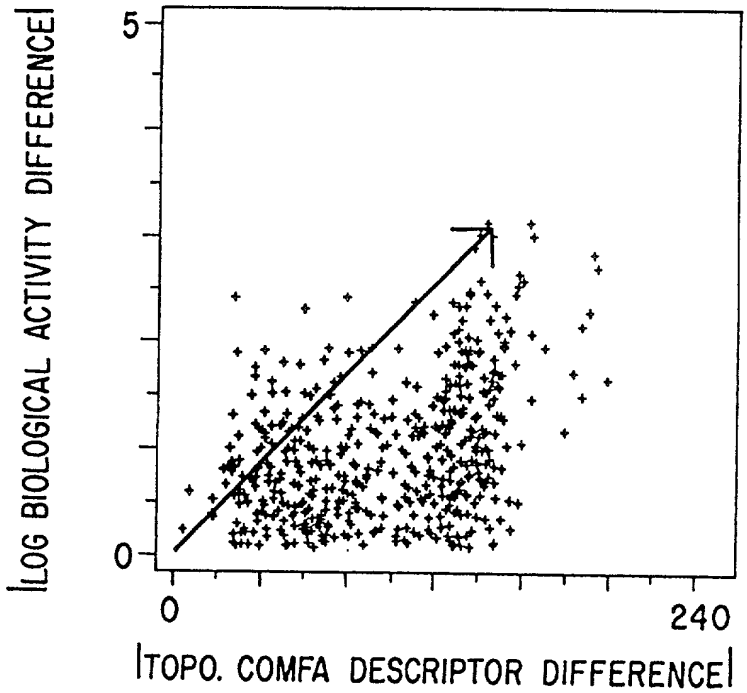


FIG. 10(b)

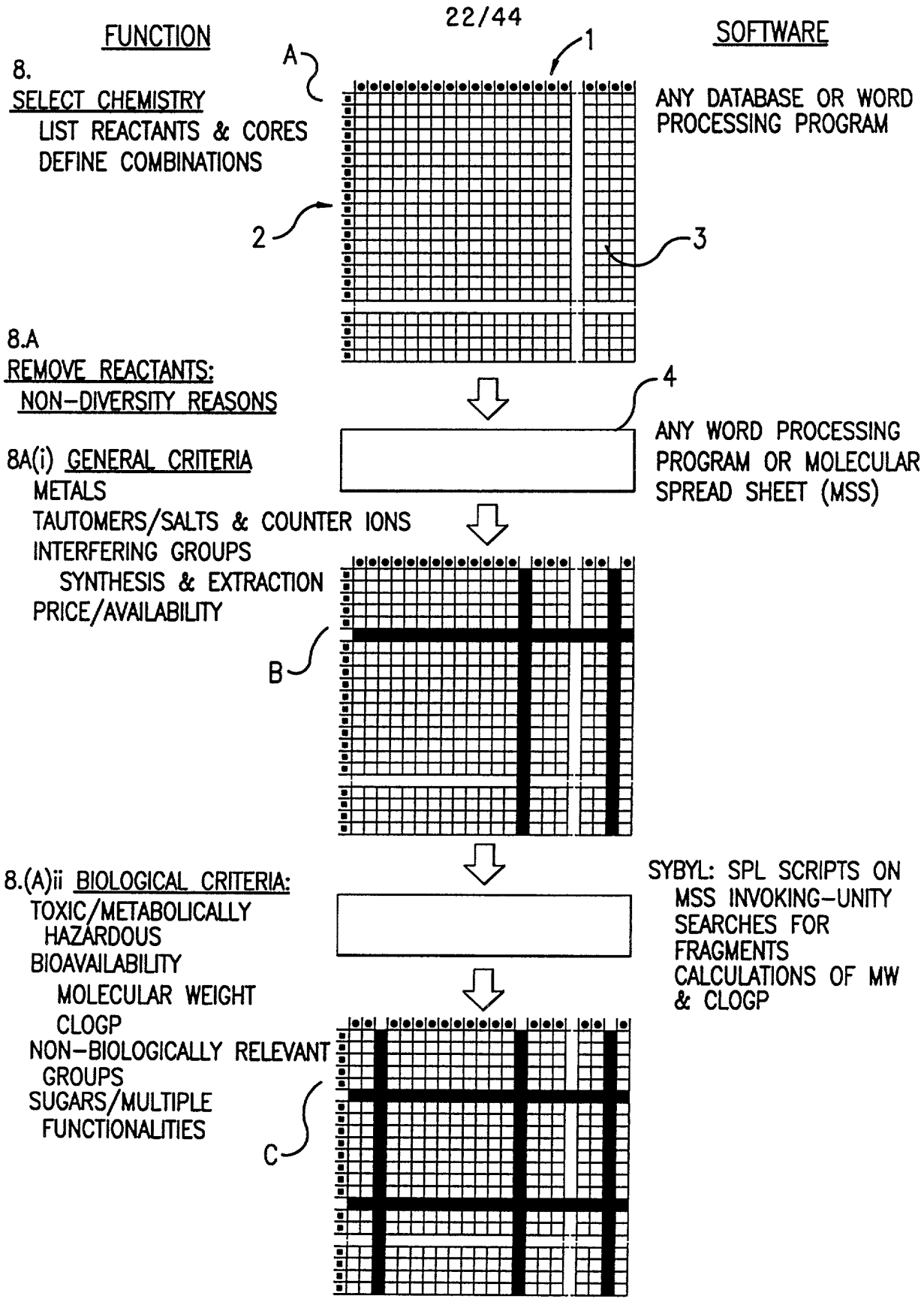


FIG.11(a)

WO 96/09548 PCT/US95/12504

8B

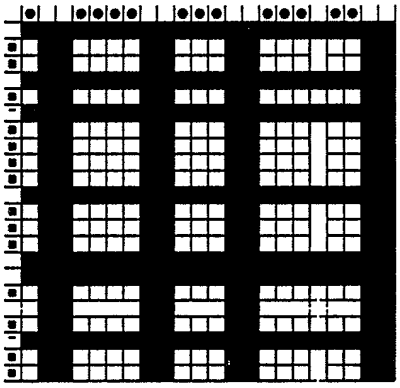
REMOVE NON-DIVERSE REACTANTS:

3D STRUCTURE GENERATION
TOPOMERIC CONFORMER ALIGNMENT
CoMFA FIELD GENERATION:
HYDROGEN BOND FIELD GENERATION
ROTATABLE BOND FIELD ATTENUATION
CALCULATE FIELD DIFFERENCES
CLUSTER
REACTANT SELECTION FROM EACH CLUSTER

SYBYL: SELECTOR & CONCORD 3.2.1 SPECIALIZED SOFTWARE: APPENDIX "A" (SYBYL: CoMFA STERIC & MSS)

SYBYL: HIERCHICAL CLUSTER – MSS
SYLBL: MSS

D

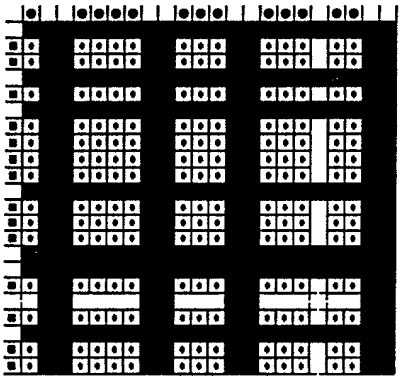


8C

COMBINE REACTANTS TO BUILD PRODUCTS

SYBYL: LEGION MSS

E



8D

REMOVE PRODUCTS:
NON-DIVERSITY REASONS

GENERAL CRITERIA:

SYBYL: SPL SCRIPTS ON MSS

F

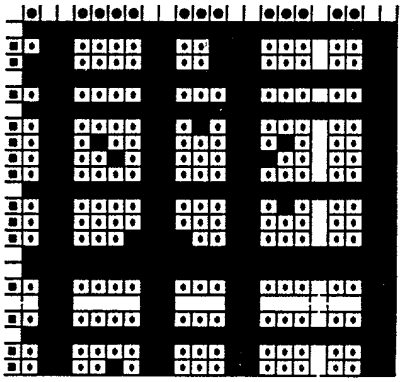


FIG.11(b)

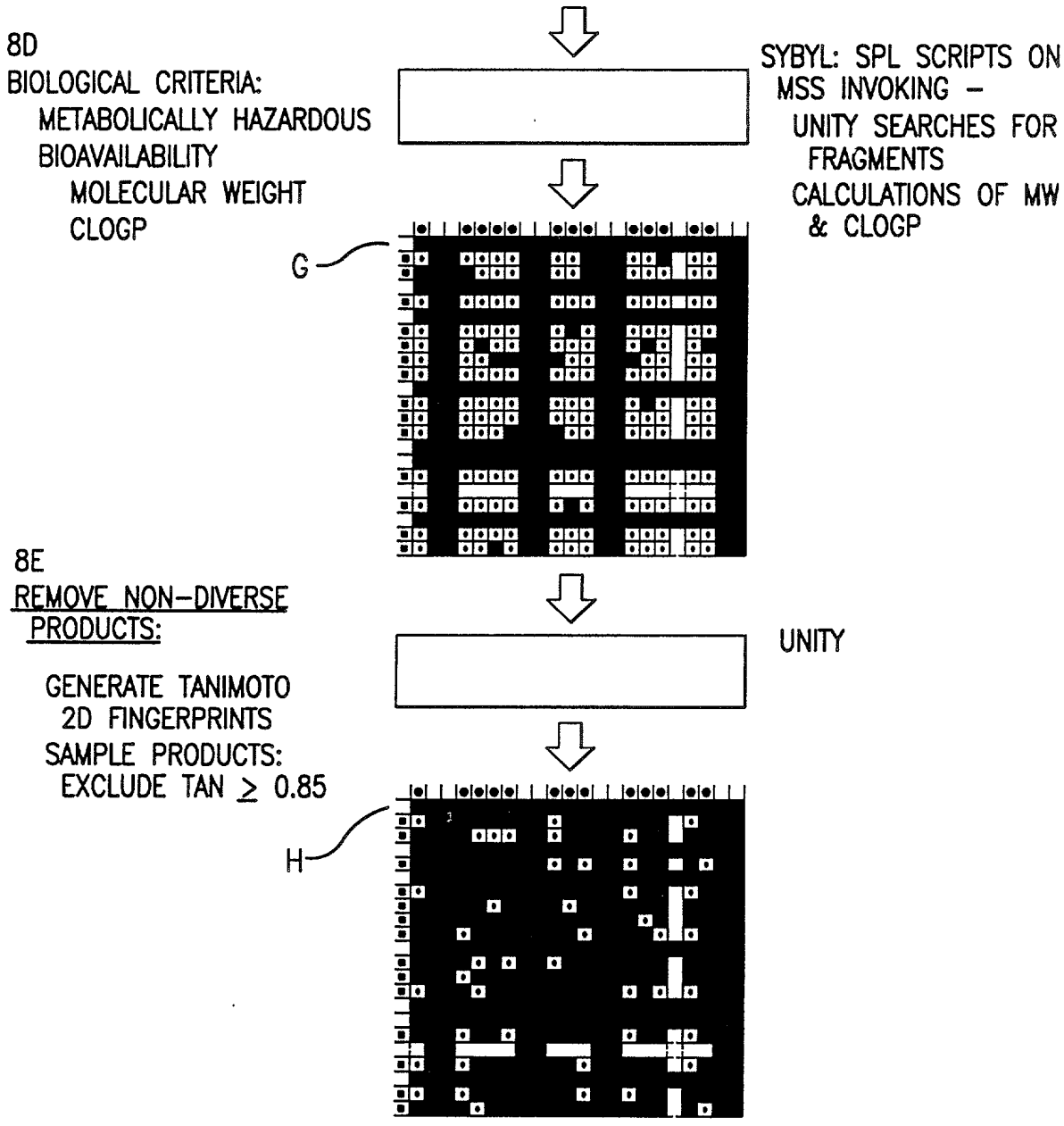

8D
BIOLOGICAL CRITERIA:
METABOLICALLY HAZARDOUS
BIOAVAILABILITY
MOLECULAR WEIGHT
CLOGP
SYBYL: SPL SCRIPTS ON MSS INVOKING –
UNITY SEARCHES FOR FRAGMENTS
CALCULATIONS OF MW & CLOGP
G
8E
REMOVE NON-DIVERSE PRODUCTS:
GENERATE TANIMOTO 2D FINGERPRINTS
SAMPLE PRODUCTS:
EXCLUDE TAN ≥ 0.85
UNITY
H

FIG.11(c)

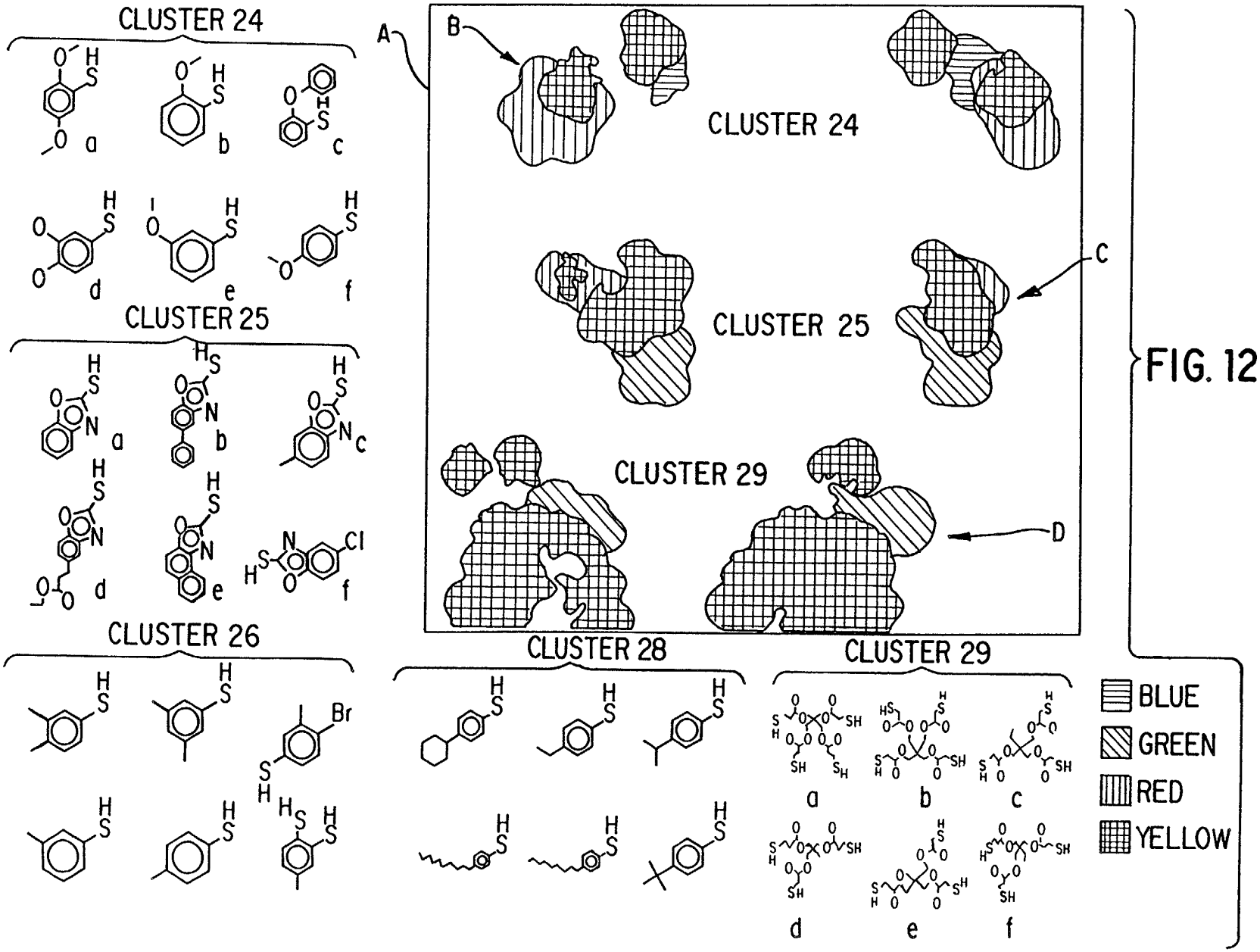

CLUSTER 24
a
b
c
d
e
f
CLUSTER 25
a
b
c
d
e
f
CLUSTER 26
A
B
C
D
CLUSTER 24
CLUSTER 25
CLUSTER 29
CLUSTER 28
CLUSTER 29
a
b
c
d
e
f
BLUE
GREEN
RED
YELLOW

FIG. 12

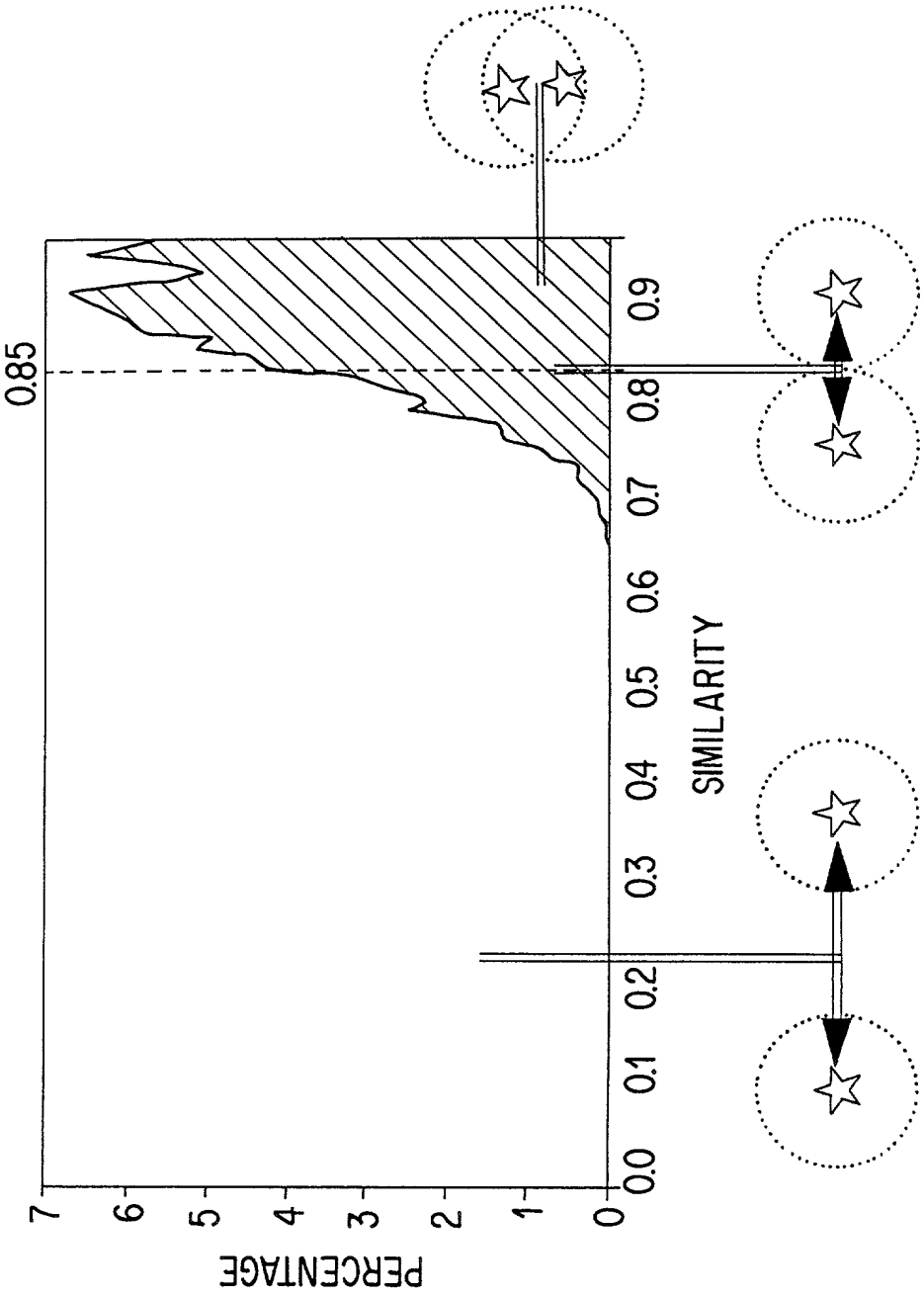


FIG.13

EP 0 969 438 A2

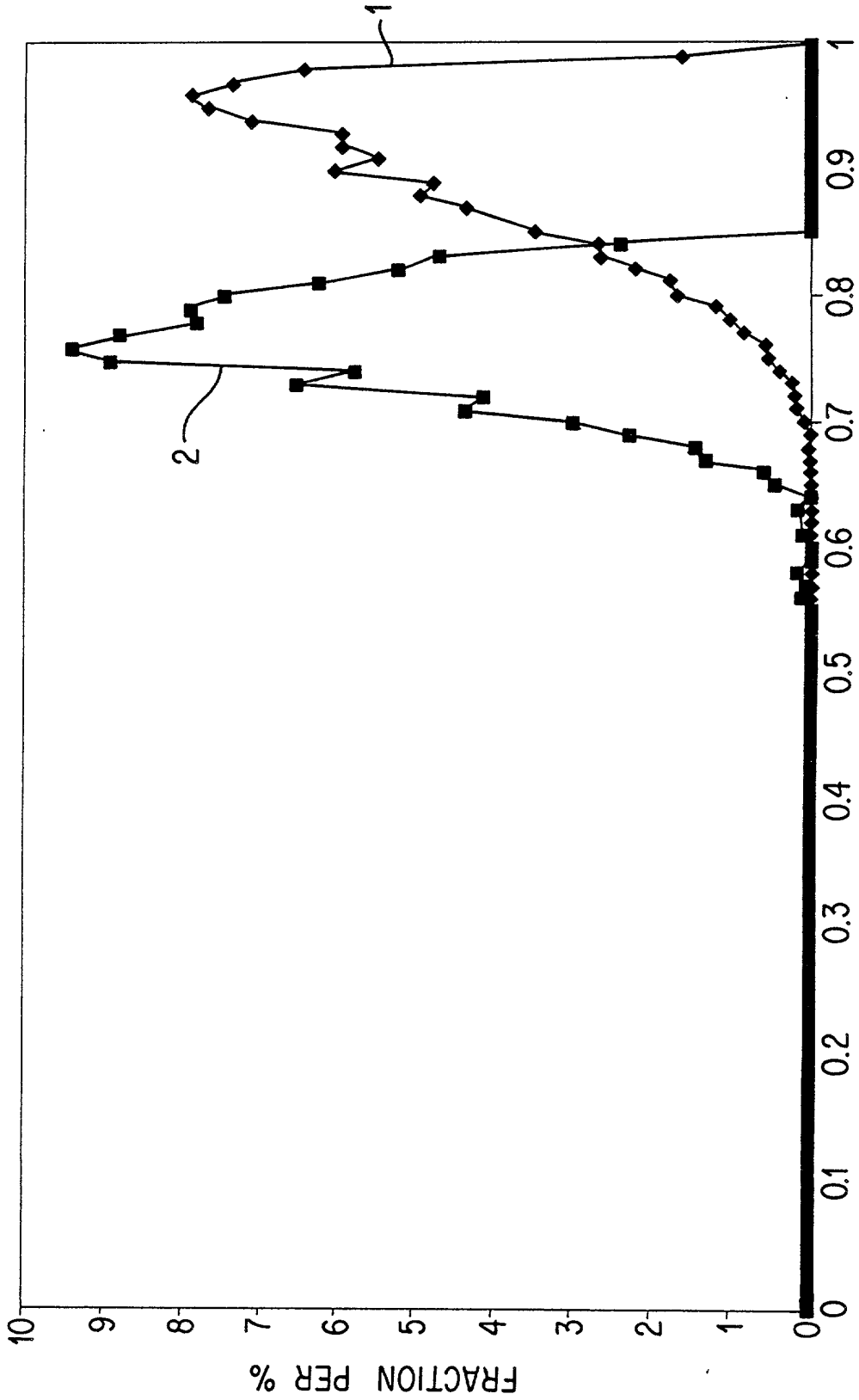


FIG.14

0595545 - 055501

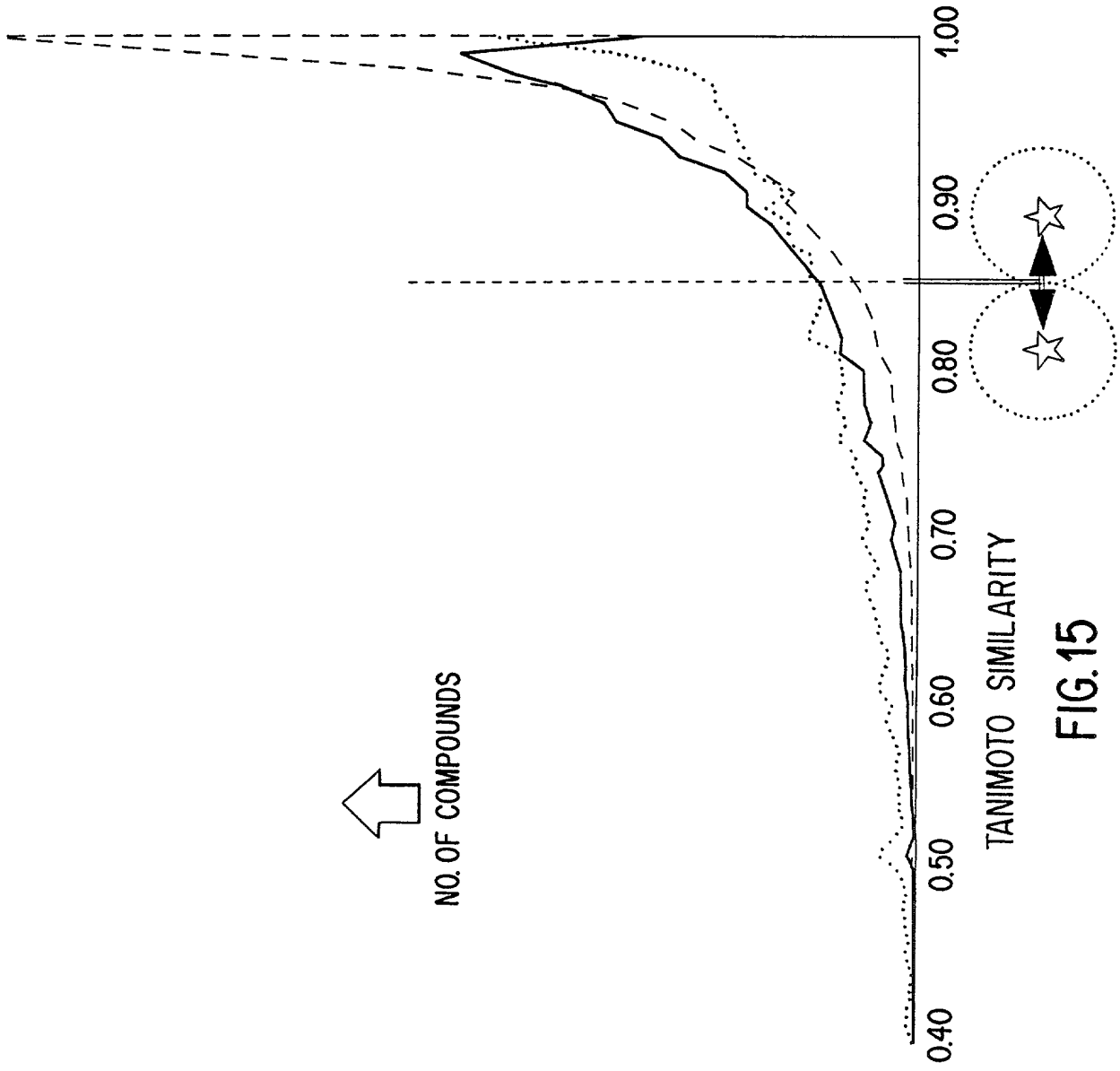


FIG.15

WO 2004/059543 PCT/US2003/040960

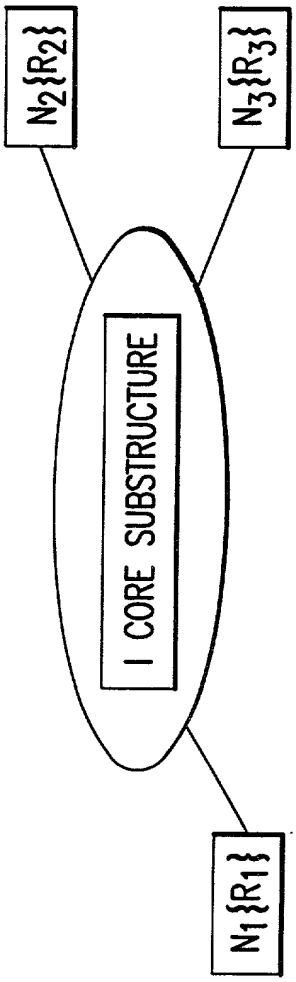


FIG.16

WO 2004/059545 PCT/US2003/040950

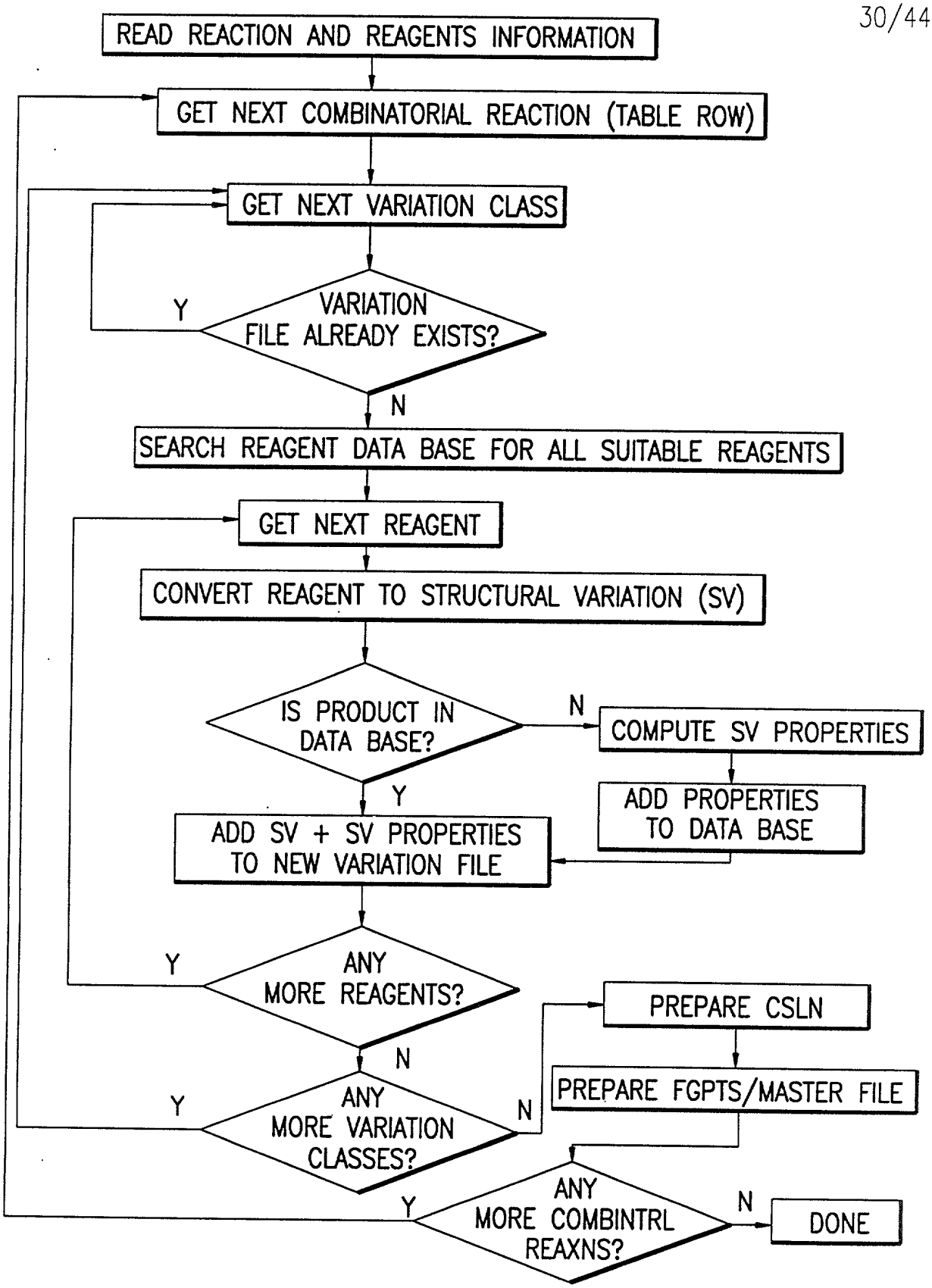

READ REACTION AND REAGENTS INFORMATION
GET NEXT COMBINATORIAL REACTION (TABLE ROW)
GET NEXT VARIATION CLASS
VARIATION FILE ALREADY EXISTS?
Y
N
SEARCH REAGENT DATA BASE FOR ALL SUITABLE REAGENTS
GET NEXT REAGENT
CONVERT REAGENT TO STRUCTURAL VARIATION (SV)
IS PRODUCT IN DATA BASE?
N
COMPUTE SV PROPERTIES
ADD PROPERTIES TO DATA BASE
Y
ADD SV + SV PROPERTIES TO NEW VARIATION FILE
ANY MORE REAGENTS?
Y
N
PREPARE CSLN
PREPARE FGPTS/MASTER FILE
ANY MORE VARIATION CLASSES?
Y
N
ANY MORE COMBINTRL REAXNS?
Y
N
DONE

FIG.17

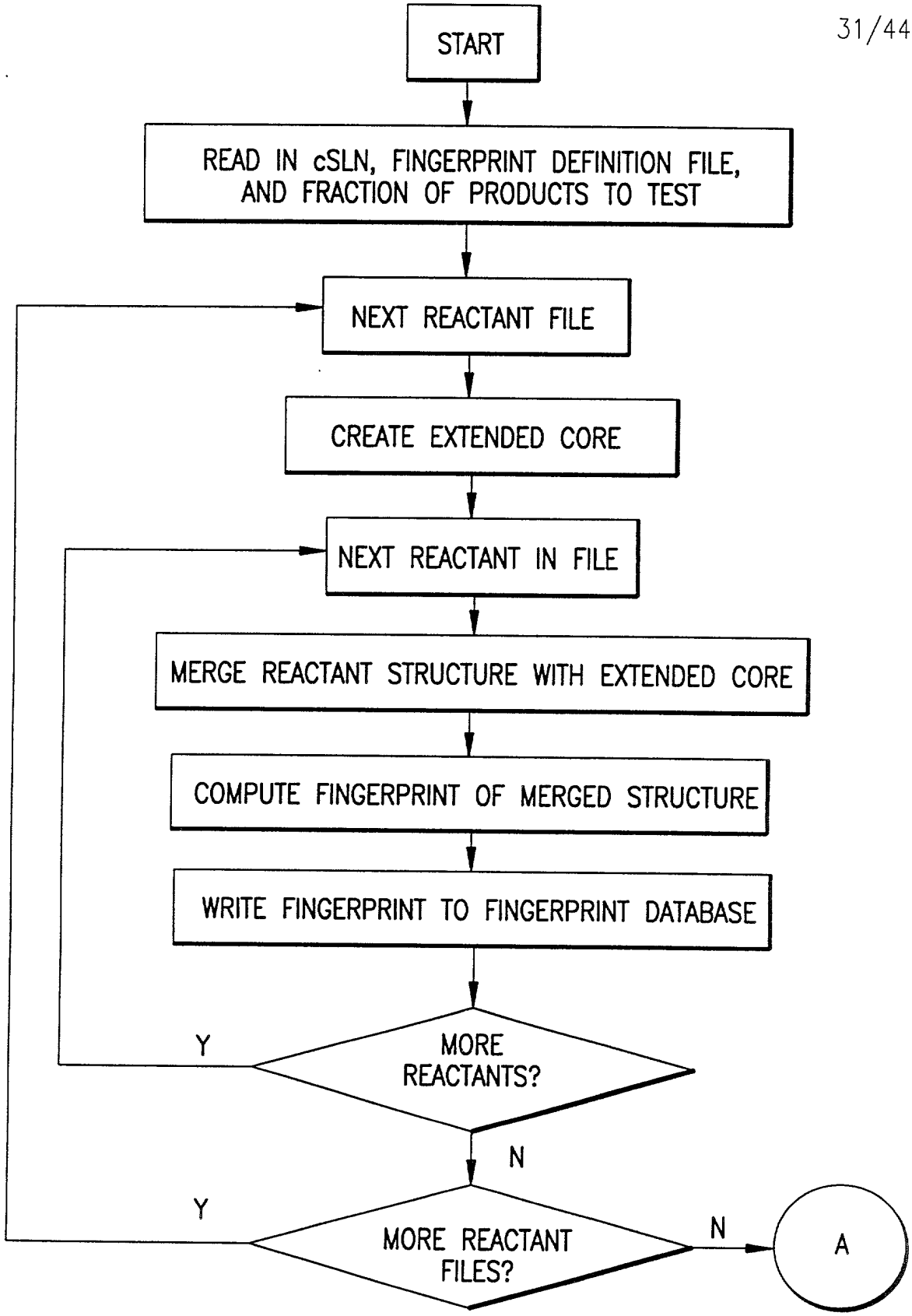

START
READ IN cSLN, FINGERPRINT DEFINITION FILE, AND FRACTION OF PRODUCTS TO TEST
NEXT REACTANT FILE
CREATE EXTENDED CORE
NEXT REACTANT IN FILE
MERGE REACTANT STRUCTURE WITH EXTENDED CORE
COMPUTE FINGERPRINT OF MERGED STRUCTURE
WRITE FINGERPRINT TO FINGERPRINT DATABASE
MORE REACTANTS?
Y
N
MORE REACTANT FILES?
Y
N
A

FIG.18

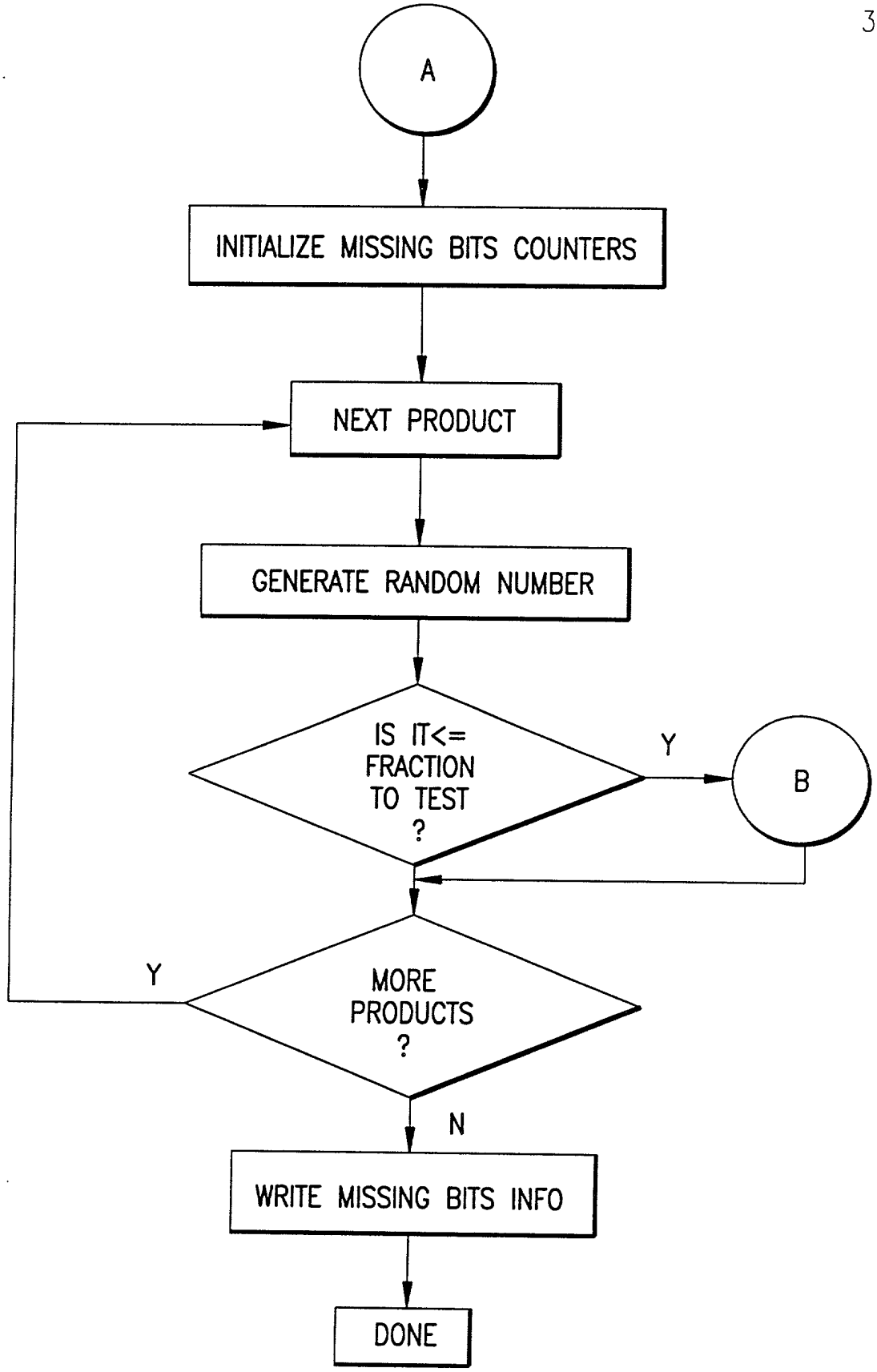


FIG.19

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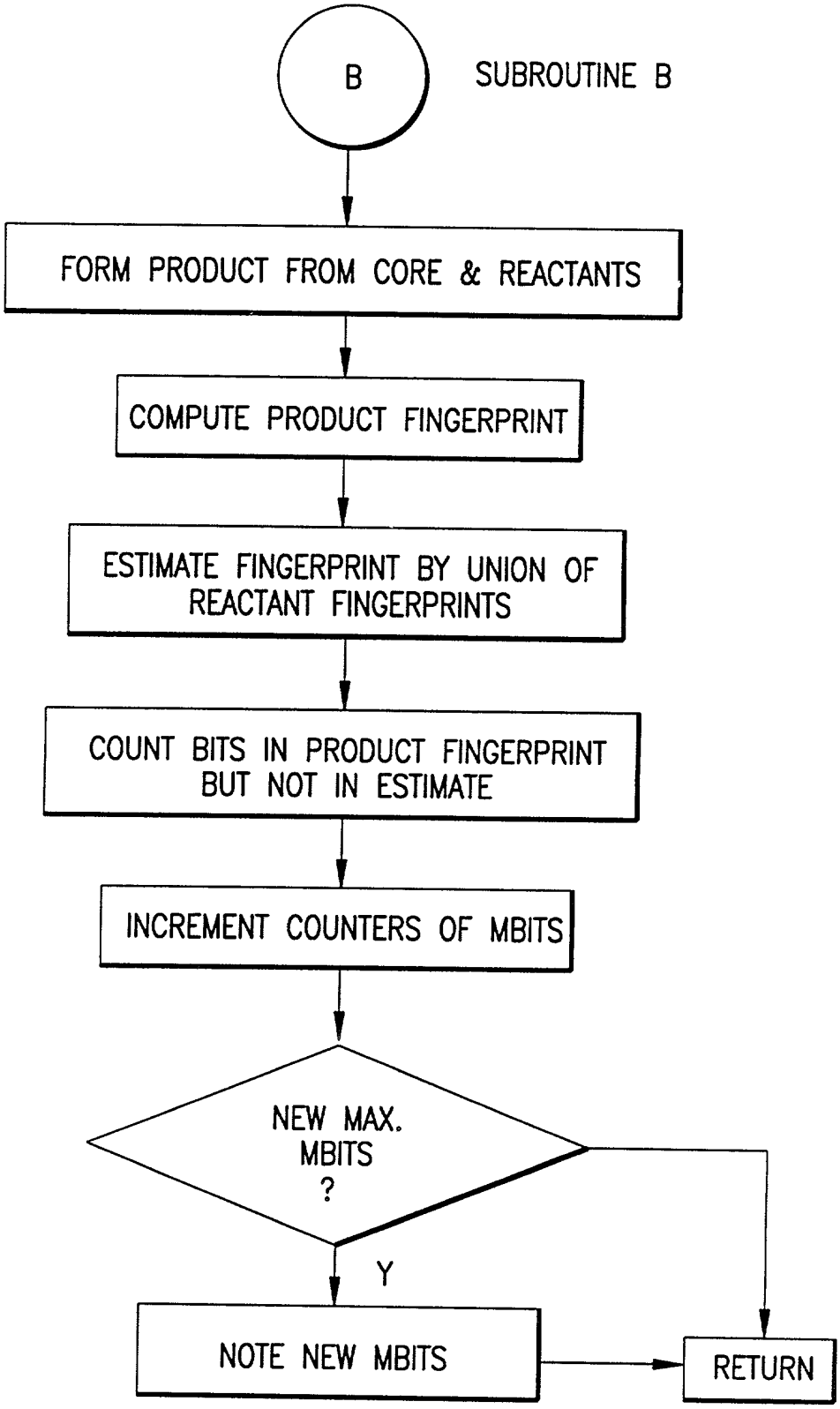
B
SUBROUTINE B
FORM PRODUCT FROM CORE & REACTANTS
COMPUTE PRODUCT FINGERPRINT
ESTIMATE FINGERPRINT BY UNION OF REACTANT FINGERPRINTS
COUNT BITS IN PRODUCT FINGERPRINT BUT NOT IN ESTIMATE
INCREMENT COUNTERS OF MBITS
NEW MAX. MBITS ?
Y
NOTE NEW MBITS
RETURN

FIG.20

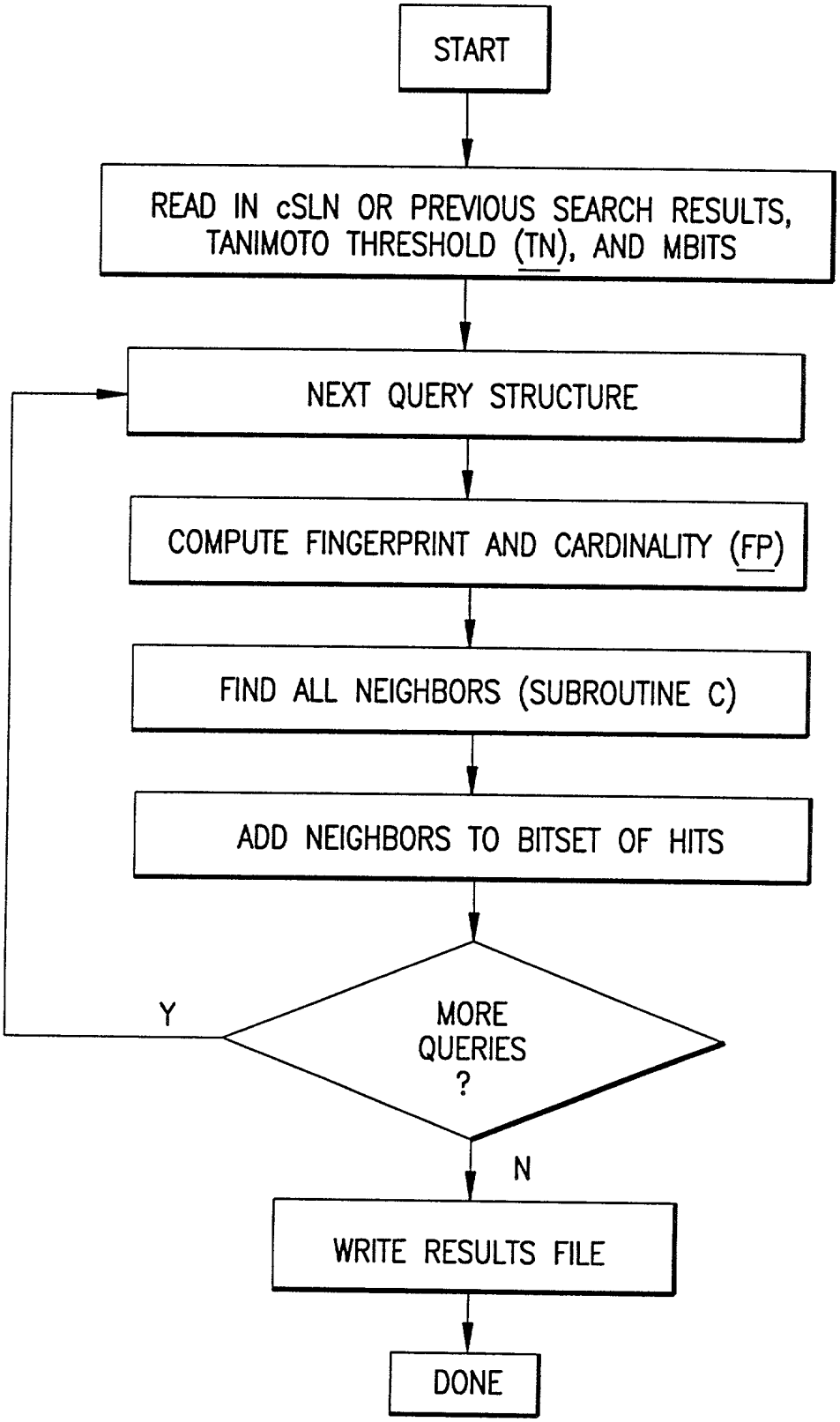
START
READ IN cSLN OR PREVIOUS SEARCH RESULTS, TANIMOTO THRESHOLD (TN), AND MBITS
NEXT QUERY STRUCTURE
COMPUTE FINGERPRINT AND CARDINALITY (FP)
FIND ALL NEIGHBORS (SUBROUTINE C)
ADD NEIGHBORS TO BITSET OF HITS
MORE QUERIES ?
Y
N
WRITE RESULTS FILE
DONE

FIG.21

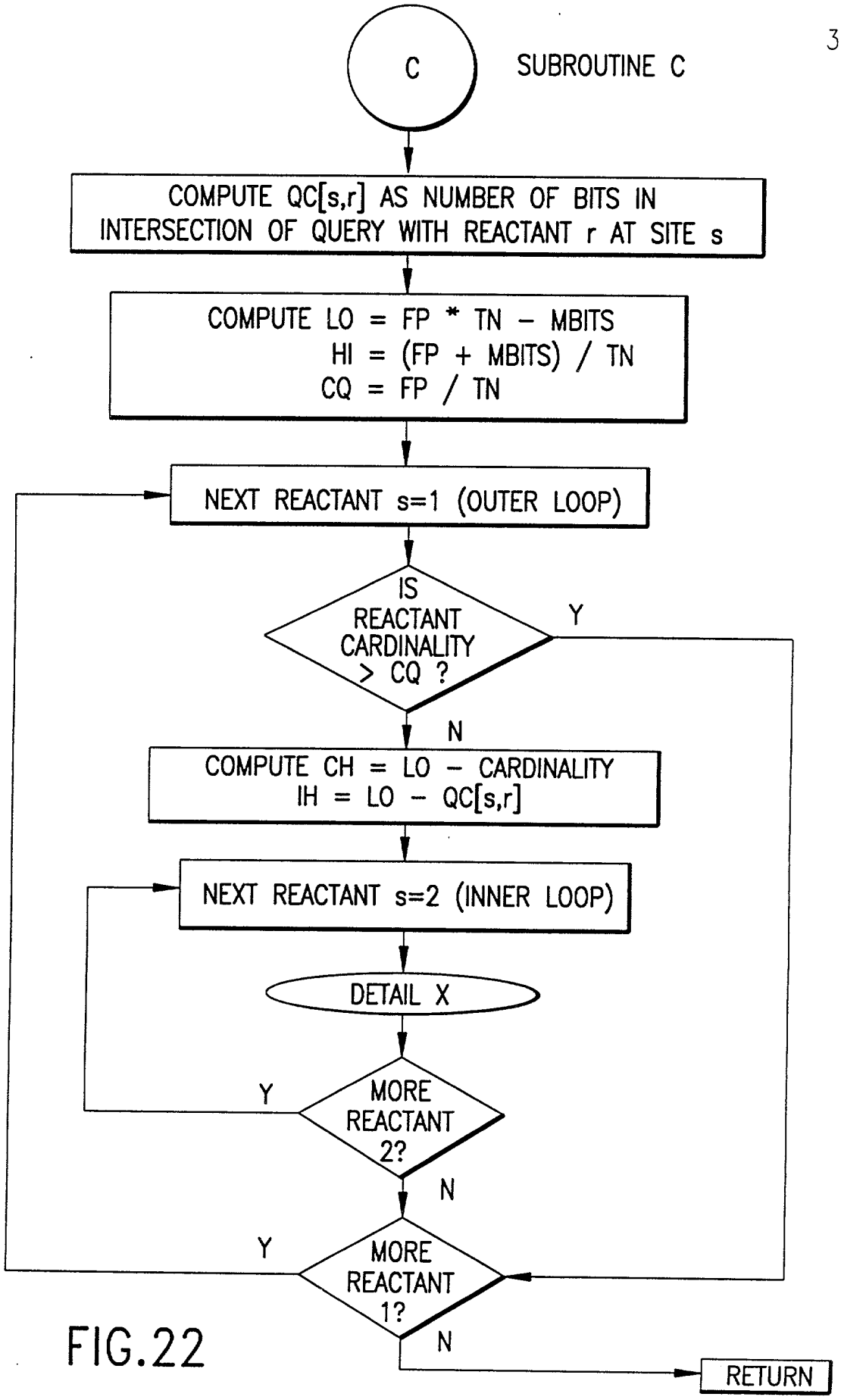
C
SUBROUTINE C
COMPUTE QC[s,r] AS NUMBER OF BITS IN INTERSECTION OF QUERY WITH REACTANT r AT SITE s
COMPUTE LO = FP * TN – MBITS
HI = (FP + MBITS) / TN
CQ = FP / TN
NEXT REACTANT s=1 (OUTER LOOP)
IS REACTANT CARDINALITY > CQ ?
Y
N
COMPUTE CH = LO – CARDINALITY
IH = LO – QC[s,r]
NEXT REACTANT s=2 (INNER LOOP)
DETAIL X
MORE REACTANT 2?
Y
N
MORE REACTANT 1?
Y
N
RETURN

FIG.22

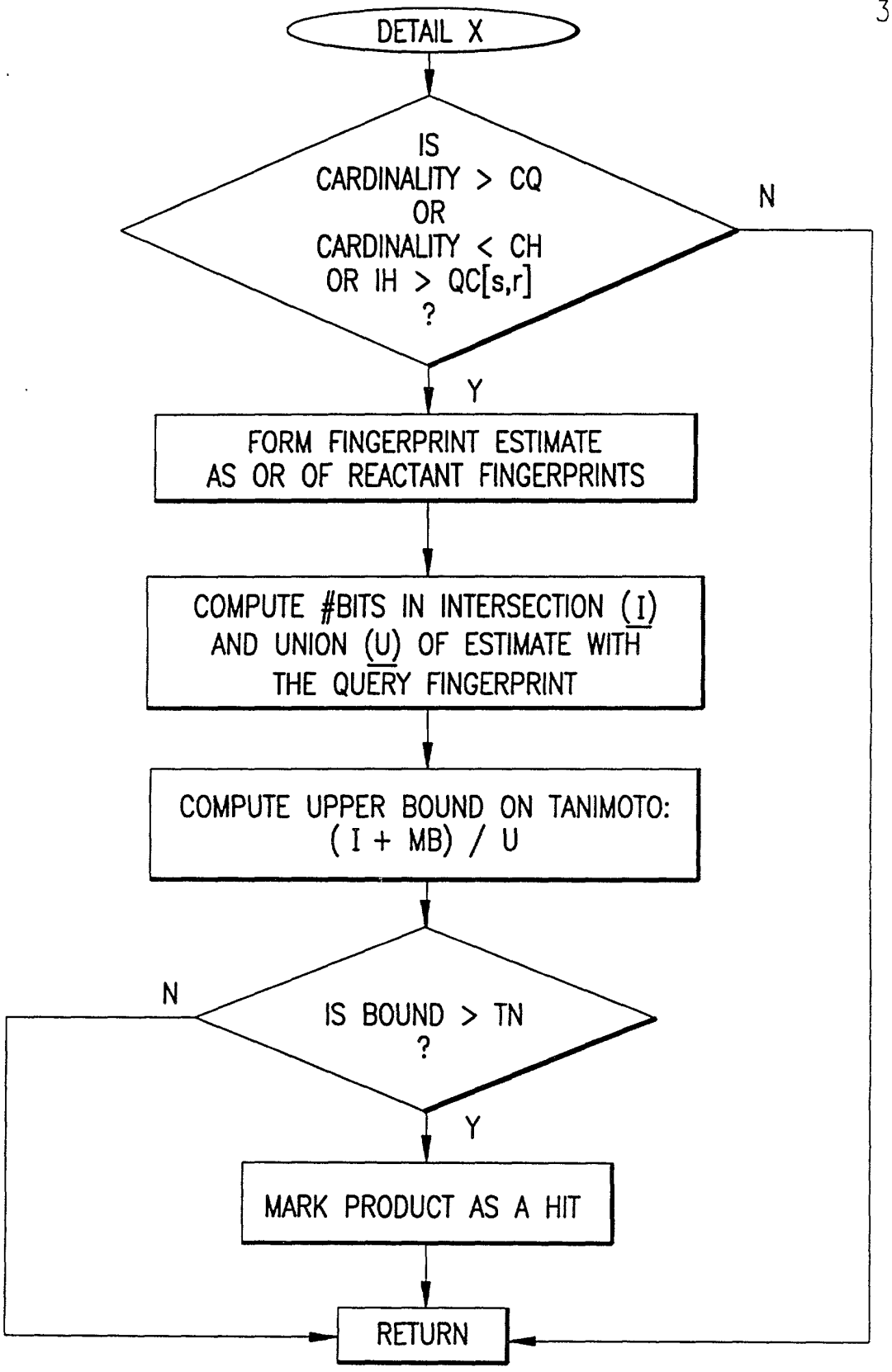

FIG.23

0606543 - 050502

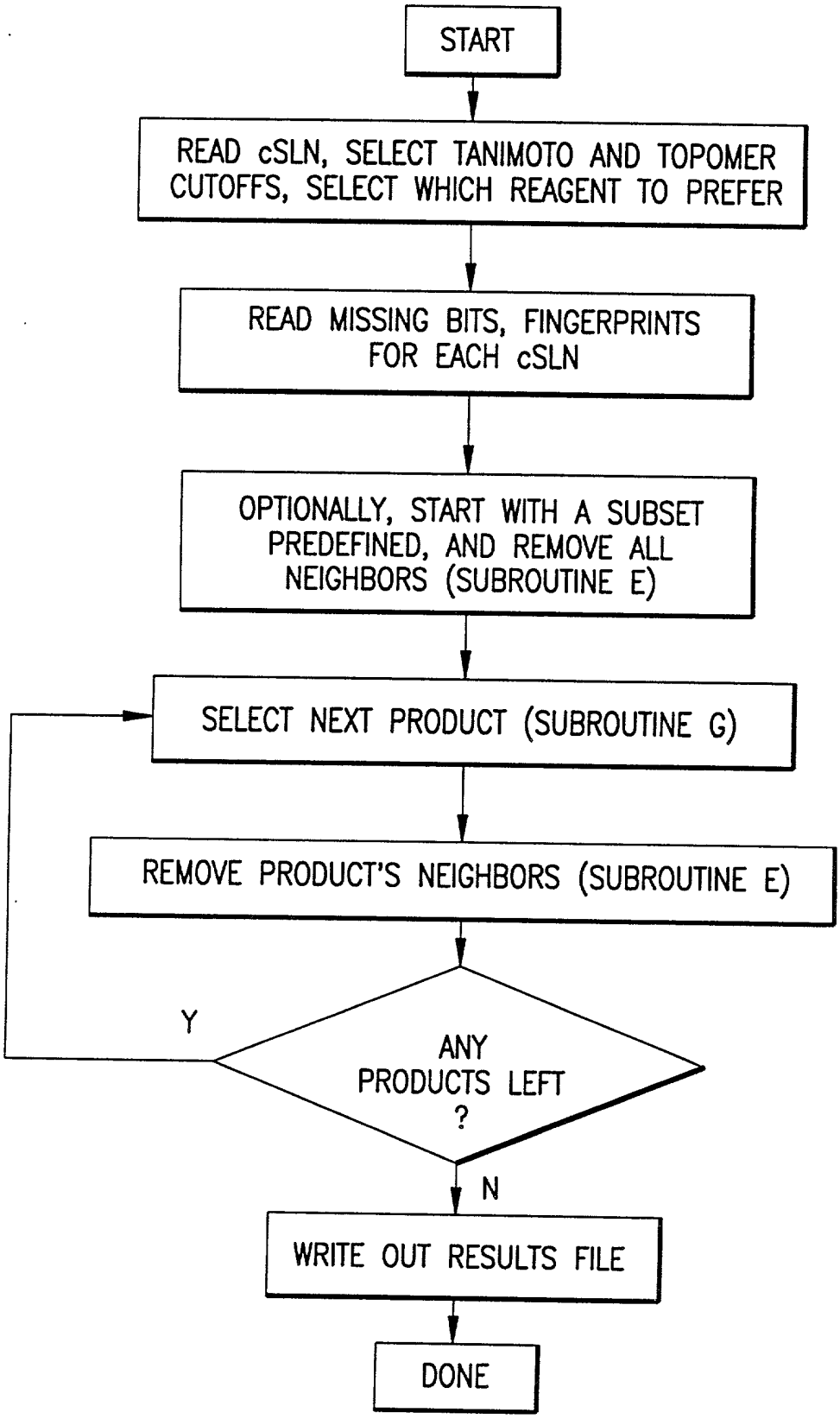

FIG.24

WO 00/69815 PCT/US00/13504

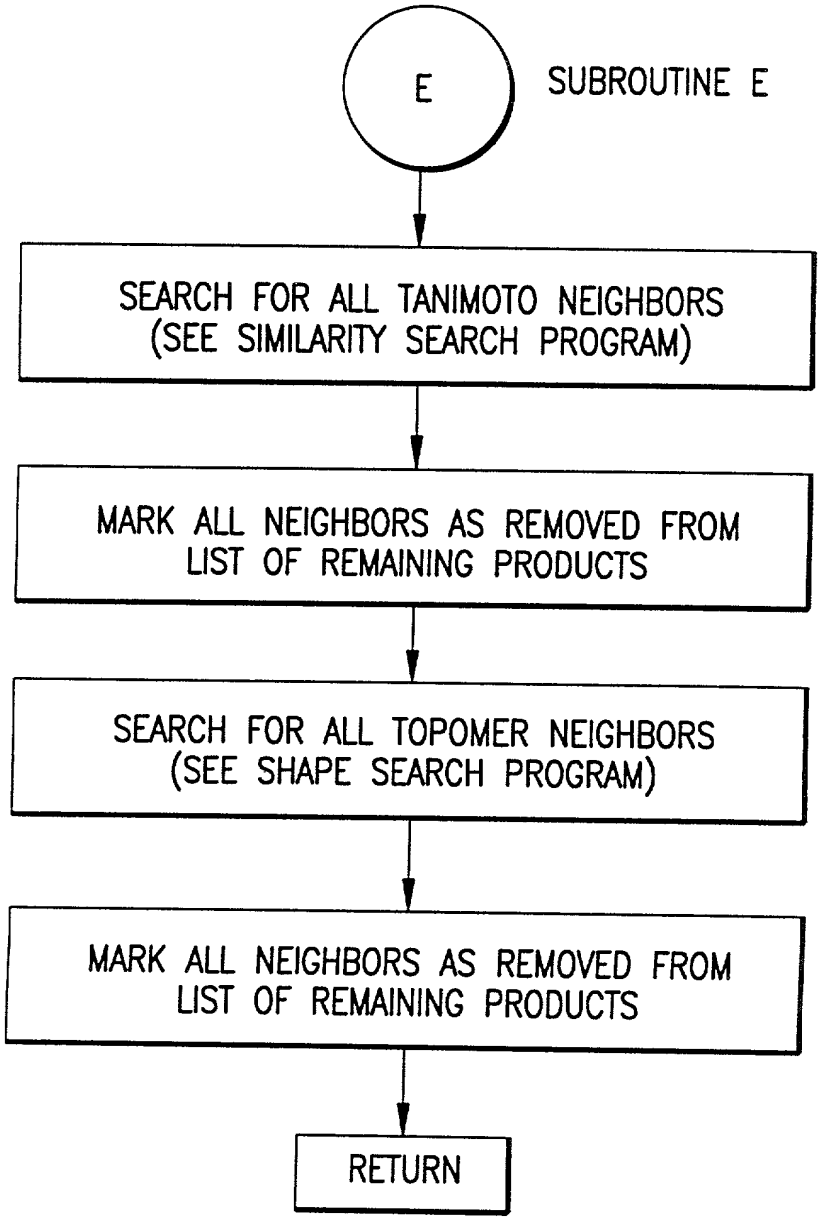

FIG.25

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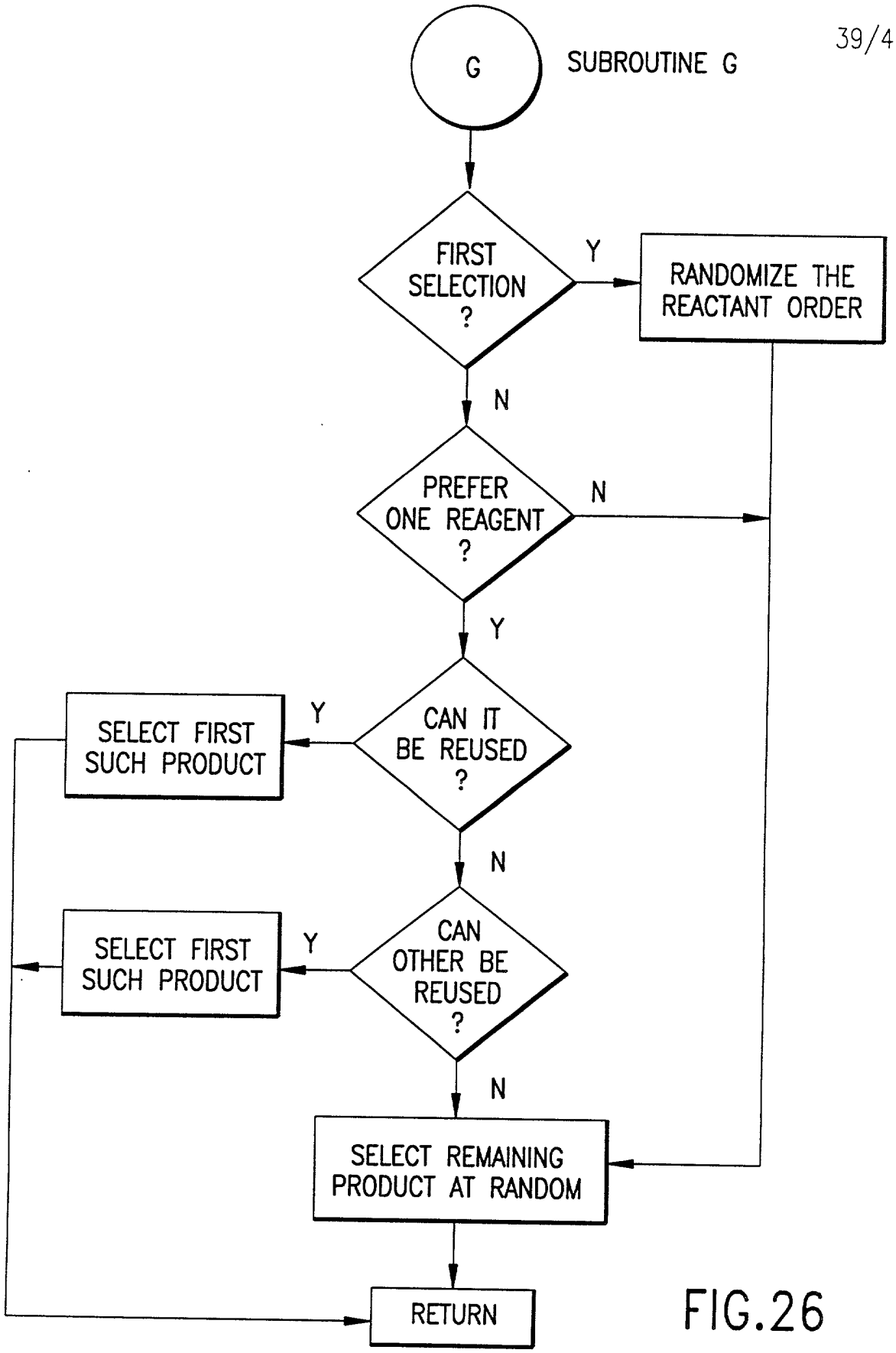

FIG.26

WO 96/06408 PCT/US95/10501

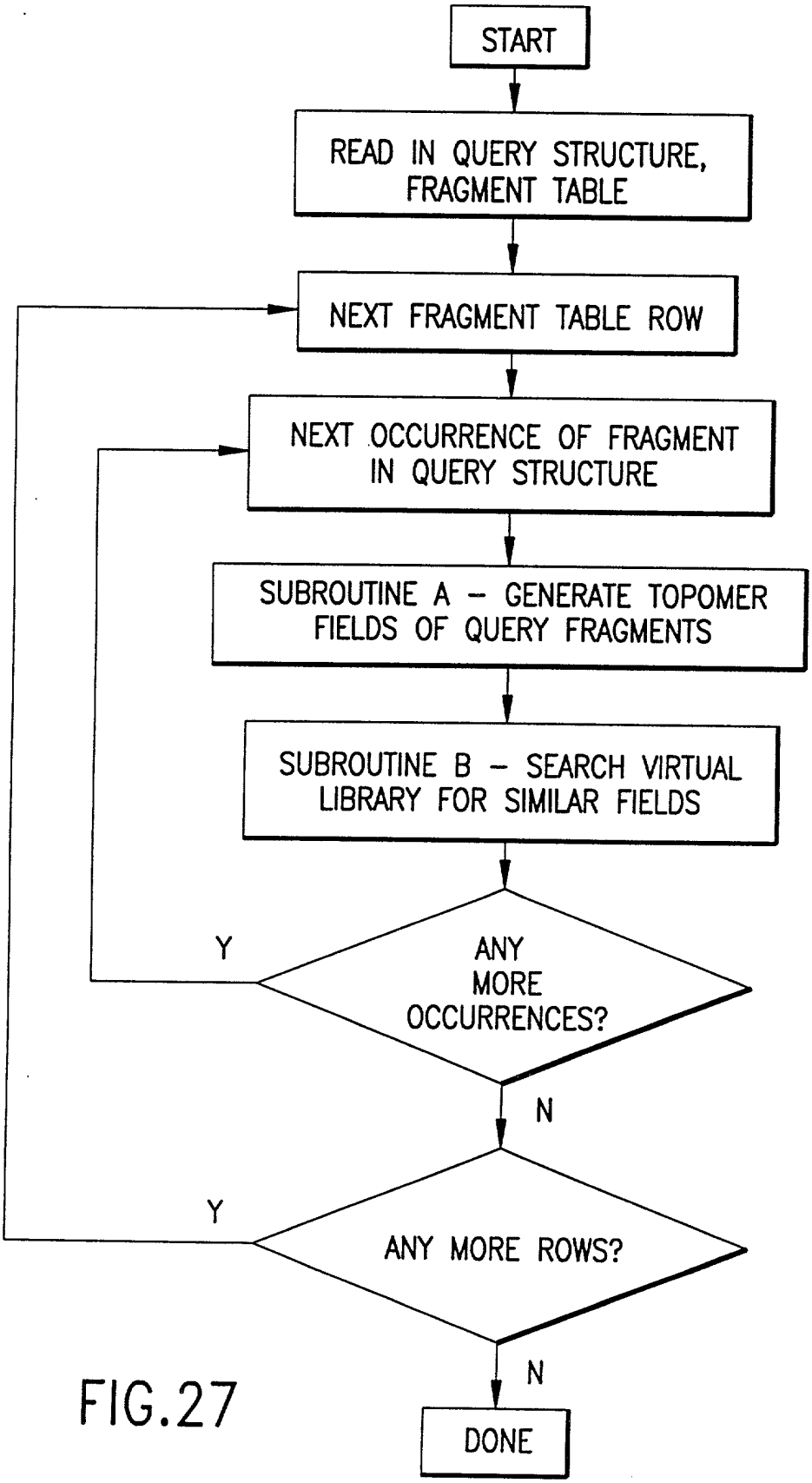
START
READ IN QUERY STRUCTURE, FRAGMENT TABLE
NEXT FRAGMENT TABLE ROW
NEXT OCCURRENCE OF FRAGMENT IN QUERY STRUCTURE
SUBROUTINE A – GENERATE TOPOMER FIELDS OF QUERY FRAGMENTS
SUBROUTINE B – SEARCH VIRTUAL LIBRARY FOR SIMILAR FIELDS
ANY MORE OCCURRENCES?
Y
N
ANY MORE ROWS?
Y
N
DONE

FIG.27

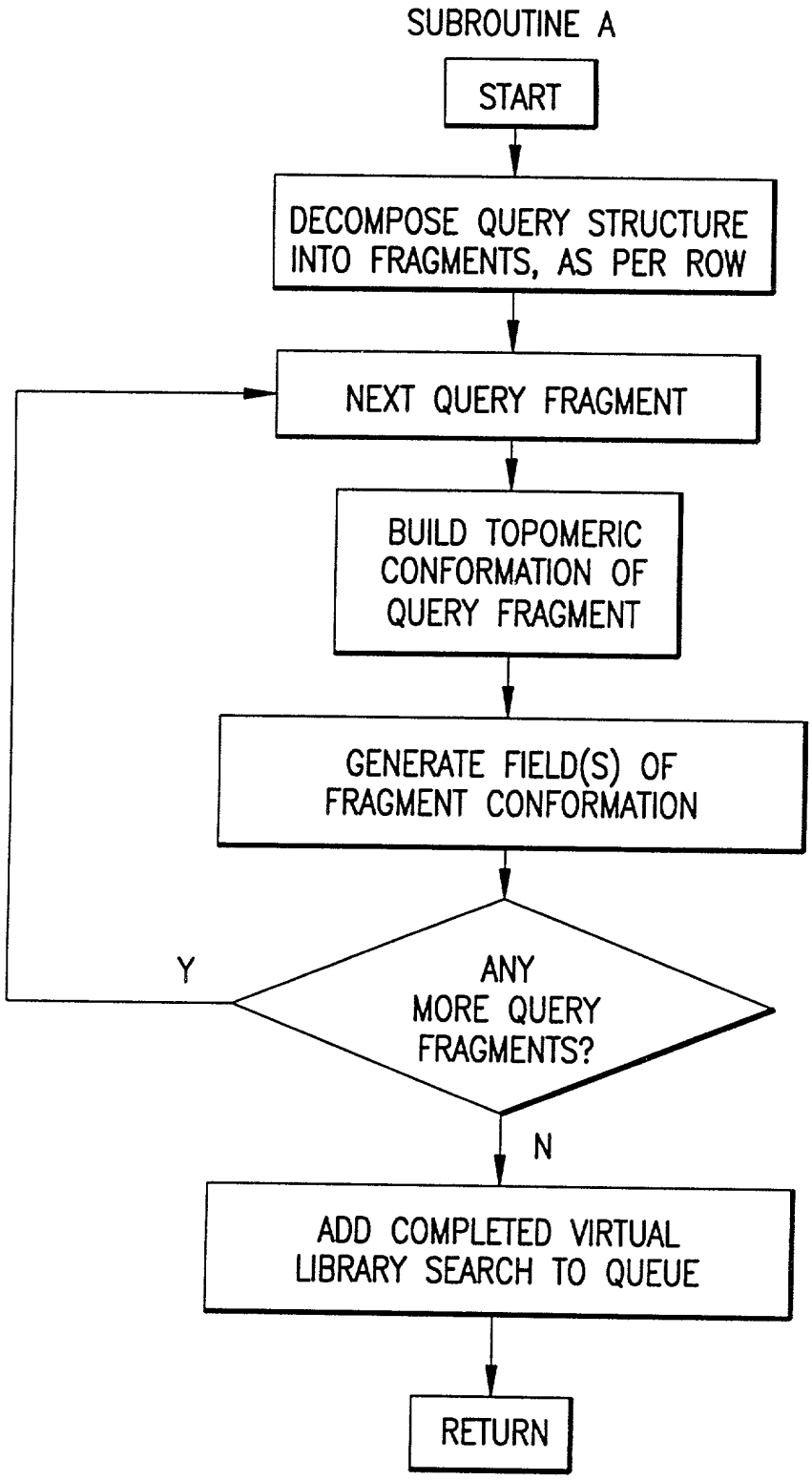
SUBROUTINE A
START
DECOMPOSE QUERY STRUCTURE INTO FRAGMENTS, AS PER ROW
NEXT QUERY FRAGMENT
BUILD TOPOMERIC CONFORMATION OF QUERY FRAGMENT
GENERATE FIELD(S) OF FRAGMENT CONFORMATION
ANY MORE QUERY FRAGMENTS?
Y
N
ADD COMPLETED VIRTUAL LIBRARY SEARCH TO QUEUE
RETURN

FIG.28

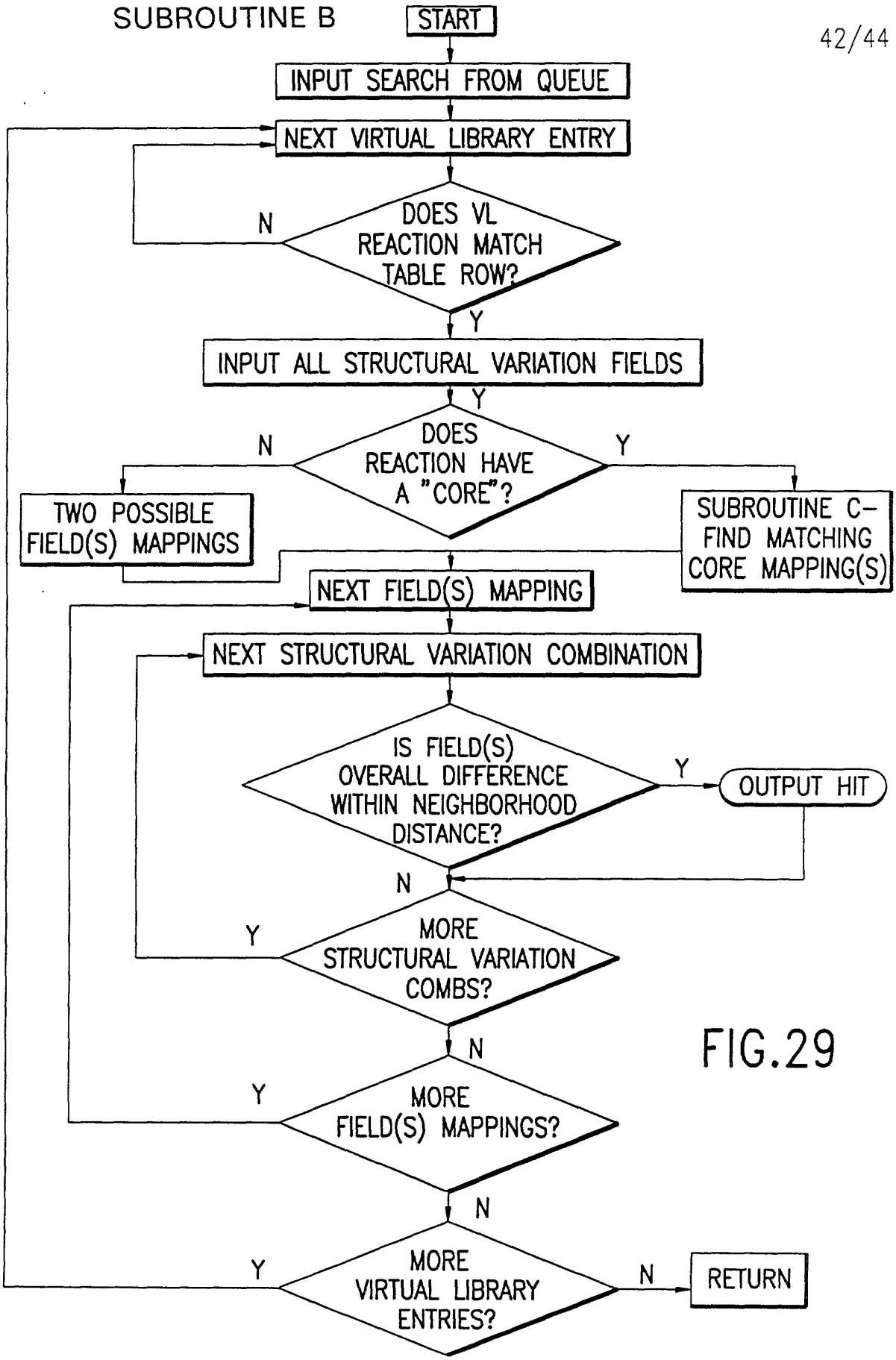

FIG.29

0606545.0606501

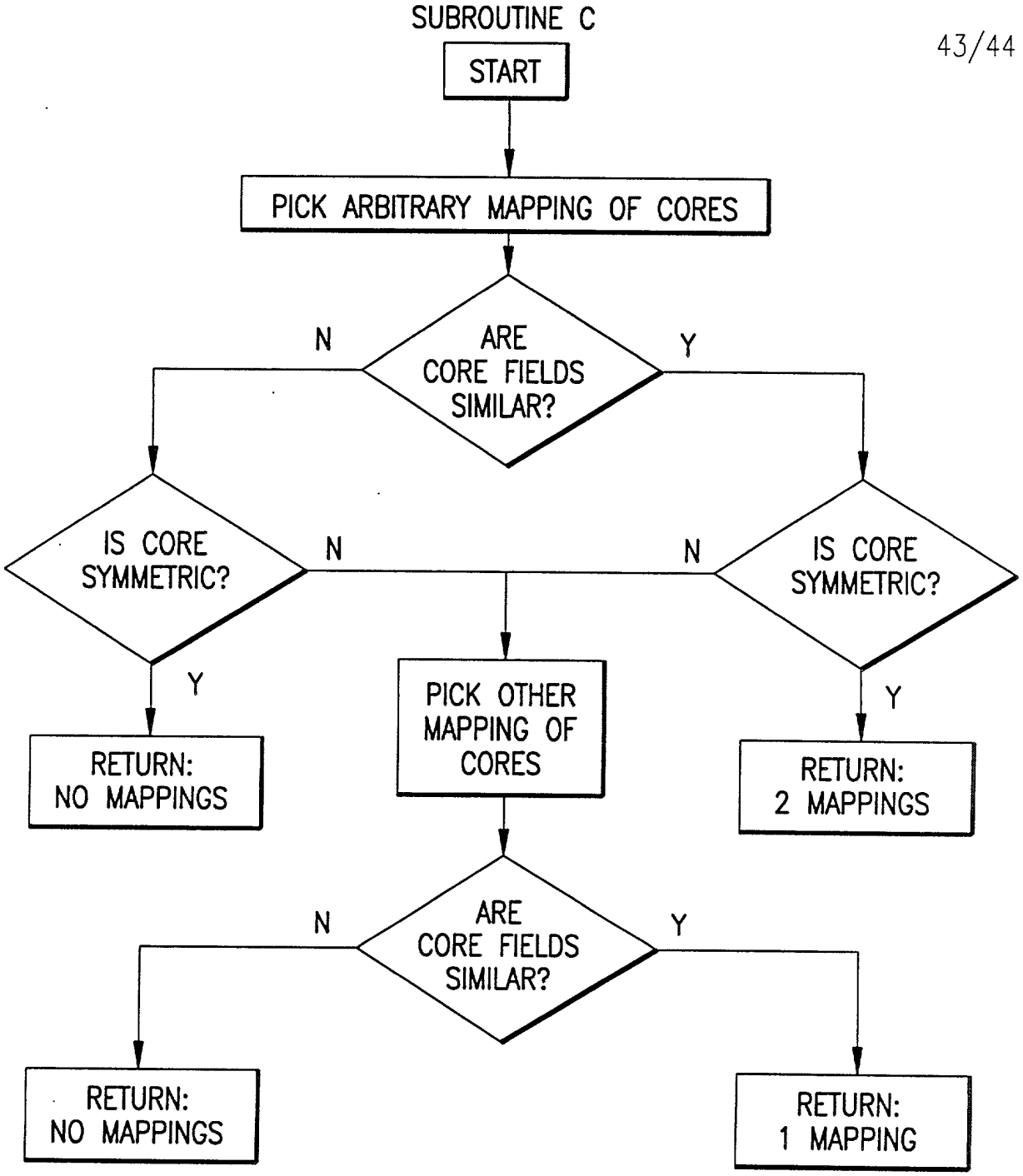
SUBROUTINE C
START
PICK ARBITRARY MAPPING OF CORES
ARE CORE FIELDS SIMILAR?
N
Y
IS CORE SYMMETRIC?
N
Y
RETURN: NO MAPPINGS
IS CORE SYMMETRIC?
N
Y
RETURN: 2 MAPPINGS
PICK OTHER MAPPING OF CORES
ARE CORE FIELDS SIMILAR?
N
Y
RETURN: NO MAPPINGS
RETURN: 1 MAPPING

FIG.30

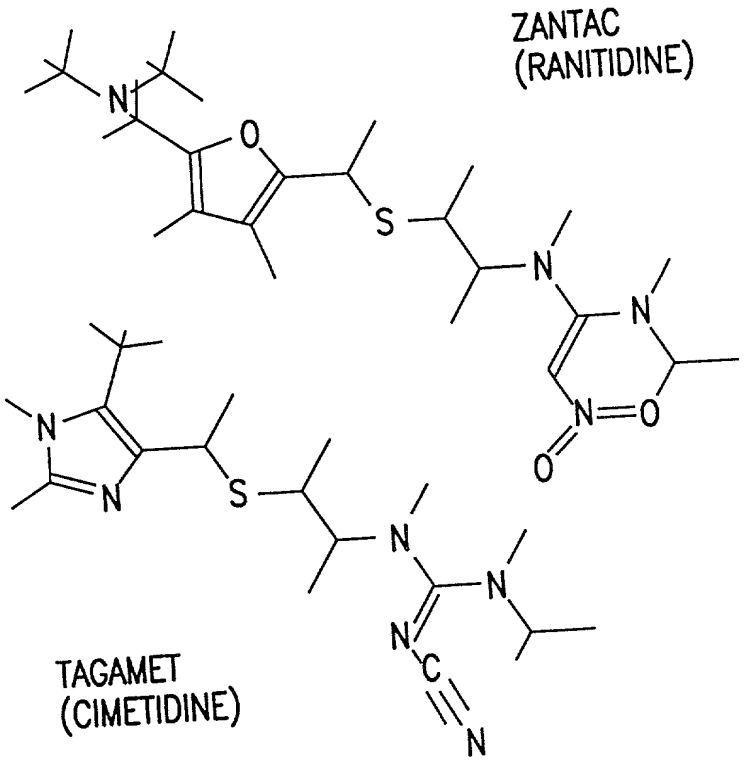

FIG.31